Study Title

COMBINED CHRONIC TOXICITY/ONCOGENICITY STUDY 2-YEAR ORAL GAVAGE STUDY IN RATS

Laboratory Project ID:

Volume 1 of 13

NUMBER OF PAGES IN VOLUME: 233

TEST GUIDELINES:
- U.S. EPA Health Effects Test Guidelines OPPTS 870.4300 Combined Chronic Toxicity/Carcinogenicity (1998)
- OECD Guidelines for the Testing of Chemicals Section 4 (No. 453) Health Effects (2009)
- JMAFF Japan Agricultural Chemicals Regulation Law 12 Nousan No. 8147 (2000)
- EEC Methods for the Determination of Toxicity Method B.33 Combined Chronic/Carcinogenicity test, Directive 88/302/EC (1988)

AUTHOR:

STUDY COMPLETED ON: March 28, 2013

APPLICANT/SPONSOR:

PERFORMING LABORATORY:

WORK REQUEST NUMBER:

SERVICE CODE NUMBER:

STUDY NUMBER:

below. Deviations from the protocol that did not affect the quality or integrity of the study are presented in Appendix N. This report accurately reflects the raw data obtained during the performance of this study.

On Day 637, the technician performing the detailed clinical observations was not yet documented as proficient in this function. The training records for this technician indicated that they were introduced to the function, but were not signed off on the function. No trainer was logged in to the computer session with this technician. The technician became proficient in this function on the day of occurrence and was signed off. No errors resulted in this deviation and the technician was subsequently found to be proficient, therefore this does not impact the study outcome.

28-Mar-2013
Date

Date

Typed name of signer: _____

QUALITY ASSURANCE STATEMENT

Below are the inspections conducted by the Quality Assurance Department and the dates the inspections were reported to the Study Director and Test Facility Management for

Date(s) of Inspection	Study Phase Inspected	Date(s) Reported to Study Director and Test Facility Management
07/13/2010	Protocol	08/10/2010
07/28/2010	Vehicle Dispensation	08/10/2010
07/28/2010	Test Material Preparation	08/10/2010
07/28/2010	Prepared Test Material Sample Collection	07/28/2010, 08/10/2010
07/29/2010	Test Material Administration	08/10/2010
08/11/2010	Detail Clinical Examinations	09/14/2010
09/21/2010	Test Material Administration	10/12/2010
09/28/2010	Protocol Amendment 1	10/12/2010
10/20/2010	Clinical Pathology Sample Preparation: Tube Set-Up	11/19/2010
10/21/2010	Clinical Pathology Sample Collection: Blood Collection	11/19/2010
10/21/2010	Clinical Pathology Operations Blood Sample Analysis	11/19/2010
11/17/2010	Detail Clinical Examinations	12/14/2010
11/17/2010	Test Material Administration	12/14/2010
11/30/2010	Protocol Amendment 2	12/14/2010
11/30/2010	Protocol Amendment 3	12/14/2010
12/20/2010	Test Material Administration	01/11/2011
01/26/2011	Clinical Pathology Sample Preparation: Urine Container Set-up	02/08/2011
01/27/2011	Clinical Pathology Sample Collection: Urine Collection	02/08/2011
01/27/2011	Clinical Pathology Operations Urine Sample Analysis	02/08/2011
02/17/2011	Test Material Administration	03/08/2011, 04/27/2011

Date(s) of Inspection	Study Phase Inspected	Date(s) Reported to Study Director and Test Facility Management
02/17/2011	Body Weight Measurements	03/08/2011, 04/27/2011
03/25/2011	Protocol Amendment 4	04/21/2011
03/29/2011	Test Material Administration	04/21/2011
03/31/2011 to 04/07/2011	Data Review	04/07/2011, 04/12/2011
04/26/1011	Test Material Administration	04/26/2011
05/16/2011 to 05/20/2011	Necropsy Data Review	05/20/2011, 06/29/2011
05/16/2011 to 05/20/2011	Necropsy (Trimming) Data Review	05/20/2011, 06/29/2011
05/16/2011 to 05/20/2011	Histology Data Review	05/20/2011, 05/20/2011
05/16/2011 to 05/20/2011	In-life Data Review	05/20/2011, 06/29/2011
05/16/2011 to 05/20/2011	Clinical Pathology Data Review	05/20/2011, 06/29/2011
05/16/2011 to 05/20/2011	Test Material Control Data Review	05/20/2011, 06/29/2011
05/16/2011 to 05/20/2011	Animal Services Data Review	05/20/2011, 05/20/2011
05/16/2011 to 05/20/2011	Clinical Medicine Data Review	05/20/2011, 05/20/2011
05/16/2011 to 05/20/2011	Pathology Data Review	05/20/2011, 05/20/2011
06/01/2011 to 06/02/2011	Test Material Administration In-process Inspection	06/02/2011, 06/02/2011
07/22/2011 to 07/22/2011	In-life Data Review	07/22/2011, 08/10/2011
07/22/2011 to 07/22/2011	Clinical Pathology Data Review	07/22/2011, 08/10/2011
07/22/2011 to 07/22/2011	Test Material Control Data Review	07/22/2011, 08/10/2011

Date(s) of Inspection	Study Phase Inspected	Date(s) Reported to Study Director and Test Facility Management
07/22/2011 to 07/22/2011	Clinical Medicine Data Review	07/22/2011, 07/22/2011
07/22/2011 to 07/22/2011	Anatomic Pathology Data Review	07/22/2011, 07/22/2011
07/27/2011 to 07/28/2011	Test Material Preparation In-process Inspection	07/28/2011, 07/28/2011
07/28/2011 to 07/28/2011	Clinical Pathology - Urine Collection In-process Inspection	07/28/2011, 07/28/2011
08/01/2011 to 08/01/2011	Clinical Pathology - Blood Collection In-process Inspection	08/01/2011, 08/30/2011
11/03/2011 to 11/07/2011	In-life Data Review	11/07/2011, 03/07/2012
11/03/2011 to 11/07/2011	Clinical Pathology Data Review	11/07/2011, 11/07/2011
11/03/2011 to 11/07/2011	Anatomic Pathology Data Review	11/07/2011, 03/07/2012
12/27/2011 to 12/27/2011	Test Material Administration In-process Inspection	12/27/2011, 12/27/2011
01/04/2012 to 01/04/2012	Test Material Preparation In-process Inspection	01/04/2012, 01/04/2012
01/27/2012 to 01/27/2012	Test Material Administration In-process Inspection	01/27/2012, 01/27/2012
04/19/2012 to 04/25/2012	In-life Data Review	04/25/2012, 10/11/2012
04/19/2012 to 04/25/2012	Clinical Pathology Data Review	04/25/2012, 04/25/2012
04/19/2012 to 04/25/2012	Anatomic Pathology Data Review	04/25/2012, 10/03/2012
04/25/2012 to 04/25/2012	Test Material Administration In-process Inspection	04/25/2012, 05/01/2012
04/25/2012 to 04/25/2012	Detailed Clinical Examinations In-process Inspection	04/25/2012, 01/28/2013
05/30/2012 to 05/30/2012	Protocol Amendment 5	05/30/2012, 05/30/2012

Date(s) of Inspection	Study Phase Inspected	Date(s) Reported to Study Director and Test Facility Management
07/23/2012 to 07/23/2012	Test Material Administration In-process Inspection	07/23/2012, 07/23/2012
07/23/2012 to 07/23/2012	Necropsy In-process Inspection	07/23/2012, 10/11/2012
07/23/2012 to 07/23/2012	Test Material Preparation In-process Inspection	07/23/2012, 10/11/2012
07/23/2012 to 07/23/2012	Protocol Amendment 6	07/23/2012, 07/23/2012
10/23/2012 to 11/09/2012	In-life/Clinical Pathology Circ Report Review	11/09/2012, 01/18/2013
10/23/2012 to 11/09/2012	Antemortem Data Review	11/09/2012, 01/28/2013
11/26/2012 to 11/26/2012	Protocol Amendment 7	11/26/2012, 11/26/2012
02/06/2013 to 02/08/2013	Postmortem Data Review	02/08/2013, 02/22/2013
02/08/2013 to 02/11/2013	Anatomic Pathology Report In-process Inspection	02/11/2013, 02/22/2013
02/15/2013 to 02/20/2013	Draft Report Review	02/20/2013, 02/22/2013
02/21/2013 to 02/21/2013	Protocol Amendment 8	02/21/2013, 02/21/2013
03/26/2013 to 03/26/2013	Protocol Amendment 9	03/26/2013, 03/26/2013
03/26/2013 to 03/27/2013	Final Report Review	03/27/2013, 0327/2013

The Quality Assurance Department has confirmed that the methods, procedures, and observations are accurately and completely described, the reported results accurately reflect the raw data, and all of the raw data have been accurately and completely transferred to the final archive.

28 MAR 2013
Date

28-Mar-2013
Date

28-MAR-2013
Date

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

STUDY INFORMATION

Substance Tested: •

•

Number:

Composition: Proprietary

Purity: 84%

Physical Characteristics: Clear and colorless liquid

Stability: The test substance appeared to be stable under the conditions of the study; no evidence of instability was observed.

Study Initiated/Completed: July 12, 2010 / March 28, 2013

Experimental Start/Termination: July 15, 2010 / March 25, 2013

In-Life Initiated/Completed: July 29, 2010 / July 20, 2012

KEY PERSONNEL

PRINCIPAL INVESTIGATOR

1. SUMMARY

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Issued Date: March 28, 2013

This study was conducted for to evaluate the potential chronic toxicity and oncogenicity of the test article, when administered via oral gavage over the major portion of the life span of the test animals. Four treatment groups of 80 male and 80 female CD® [Crl:CD(SD)] rats were administered the test article at respective dose levels of 0.1 (males only), 1, 50, and 500 (female only) mg/kg/day. One additional group of 80 animals/sex served as the control and received the vehicle, deionized water. The vehicle or test article was administered to all groups via oral gavage, once a day for up to 104 weeks, at a dose volume of 10 mL/kg/dose. Due to poor overall survival in females, all female dose groups were sacrificed at Week 101. In this report, this terminal interval will be referred to as 24 month.

Observations for morbidity, mortality, injury, and the availability of food and water were conducted twice daily (three times daily beginning in Week 53) for all animals. Observations for clinical signs and masses were conducted weekly. Body weight and body weight change were measured and recorded weekly for the first 14 weeks and then every other week thereafter. Food consumption was measured and recorded pretest (Week -1), weekly during the first 13 weeks, and for 2 week intervals starting on Week 14, and food efficiency was calculated. Ophthalmoscopic examinations were conducted all animals pretest and on all surviving animals prior to the interim and terminal necropsies. Blood and urine samples for clinical pathology evaluations were collected from designated animals at 3 (no coagulation or urine), 6, and 12 months. Peripheral blood smears were collected from designated animals at 12 and 18 months and prior to termination. At study termination (12 and 24 months), necropsy examinations were performed, organ weights were recorded, and tissues were microscopically examined.

There were no test article-related effects on survival. There were no adverse clinical or ophthalmological observations attributed to test article exposure.

No adverse, test article-related effects on body weight or nutritional parameters were observed in males at any dose. Mean food consumption and food efficiency values were generally comparable to control throughout the study.

Exposure to 500 mg/kg/day (females) produced adverse reductions in body weight, body weight gain, and food efficiency. Mean body weight in this group was 13% below control at Week 52 (statistically significant), but was generally comparable to the control value at termination. Mean body weight gain in this group was 20% below controls over Weeks 1 to 52 but only slightly lower than the control value (not statistically significant) over the two year period. There was no test article-related effect on food consumption. The reduced body weight gain was associated with lower mean food efficiency over the first year although overall (2-year) food efficiency was comparable to controls. The body weight, body weight gain, and food efficiency

differences were considered adverse at this dose based on the magnitude of difference during the first year of exposure.

No adverse effects on body weight or nutritional parameters were observed in any other dose group.

There were no test article-related effects on survival over the course of this study. The only test article-related cause of death/morbidity was inflammation/necrosis of the kidneys in 500 mg/kg/day females. This cause of death/moribundity was assigned to animals whose early death was considered to be the result of renal papillary necrosis observed microscopically. There was no test-article related increase in masses or mass findings.

At the 3, 6, and 12 month intervals, there were mild decreases in red cell mass (erythrocytes, hemoglobin, and hematocrit) in females receiving 500 mg/kg/day (up to 28% below control). These changes were associated with an appropriate increase in reticulocytes (up to 106% above control). There were no effects on erythrocyte morphology. This collection of findings is suggestive of red cell loss or increased red cell turnover (hemolysis) although the exact mechanisms involved are unknown. All of these findings were considered test article related and adverse.

Statistically significant decreases in red cell mass were also present in males receiving 50 mg/kg/day at the 3- and 6-month interval. However, the decreases were small, did not induce statistically significant changes in reticulocytes, and were transient (no statistically significant differences at 12 months), and values in individual animals in the 50 mg/kg/day group were similar to controls. Therefore, the red cell mass changes in 50 mg/kg/day males were considered to be test article-related but nonadverse.

No other effects on hematological parameters were attributed to test article exposure in either sex at any dose or interval. There were no test article-related effects among coagulation times in either sex at any dose level. No test article-related effects among leukocytes were observed in either sex.

Increases in enzymes indicative of liver injury were observed at 12 months in males at 50 mg/kg/day, including mild increases in alanine aminotransferase (ALT) and sorbitol dehydrogenase, and were correlated with microscopic findings of minimal cystic degeneration and minimal to mild focal necrosis in the liver of males at 50 mg/kg/day. Therefore, these enzymes changes were considered test article-related and adverse. There were also mild increases in alkaline phosphatase at the 3 and 6 month intervals in males at this dose level; these increases were less than those present at 12 months and were not associated with statistically significant changes in other enzymes indicative of hepatic or hepatobiliary injury at these time points. Therefore, the changes in alkaline phosphatase at the 3 and 6 month intervals may be due in part or in whole to test article-related enzyme induction, as the test article was previously shown to produce an increase in total P450 enzyme activity in male rats at 30 mg/kg/day. There were no test article-related changes in liver enzymes in males receiving 1 or 0.1 mg/kg/day or in females at any of the dose levels tested (up to 500 mg/kg/day).

Increases in albumin were present in 50 mg/kg/day males at all intervals and in 500 mg/kg/day females at the 3-month interval. Decreases in globulin were present in 500 mg/kg/day females at all intervals (with an associated decrease in total protein at the 6-month interval). No statistically significant decreases in group means for globulin were present in males at any dose or interval; however, small decreases in individual values for these parameters in individual animals in the 50 mg/kg/day male group may have been test article-related. The changes in albumin and globulin in the high-dose male and female groups also resulted in statistically significant increases in albumin/globulin ratio in these groups at all intervals. These changes in serum proteins in high dose males and females were considered test article-related but were not considered biologically relevant based on their small magnitude and lack of association with known adverse outcomes.

Statistically significant increases in urine volume and decreases in urine specific gravity were observed at 6- and 12-months in 500 mg/kg/day females, suggestive of a minimal diuresis. Although minimal and not associated with changes in kidney-related chemistry parameters, these differences may be correlative to increased incidences and severity of chronic progressive nephropathy observed in this dose group at the 1-year interim sacrifice.

At the interim necropsy, test article-related effects included irregular surface of the kidney (500 mg/kg/day females) and increased liver weights (50 mg/kg/day males and 500 mg/kg/day females). Microscopic pathology findings in the interim sacrifice groups included minimal focal cystic degeneration and minimal to mild focal necrosis of the liver (50 mg/kg/day males), centrilobular hypertrophy of the liver (500 mg/kg/day females), and increased incidence and severity of chronic progressive nephropathy in the kidney (500 mg/kg/day females).

At termination (2-year), test article-related increases in liver weight and macroscopic observations in the kidneys (irregular surface) and liver (tan focus/foci and mass/nodule) were observed in 500 mg/kg/day females. These macroscopic observations were correlative to test article-related microscopic findings described below.

At termination, test article-related non-neoplastic microscopic changes were observed at the highest doses tested in each sex: in the liver of 50 mg/kg/day males and in the liver, kidneys, nonglandular stomach (limiting ridge), and tongue of 500 mg/kg/day females.

In the liver of males at 50 mg/kg/day, there were statistically significantly increased incidences of focal cystic degeneration, centrilobular hepatocellular hypertrophy, and centrilobular hepatocellular necrosis. Test article-related findings in the liver of 500 mg/kg/day females were similar to those noted in 50 mg/kg/day males, and also included low incidences of panlobular hepatocellular hypertrophy and individual cell hepatocellular necrosis.

Microscopic findings in the kidneys of 500 mg/kg/day females included tubular dilatation, edema of the renal papilla, transitional cell hyperplasia in the renal pelvis, tubular mineralization, renal papillary necrosis, and chronic progressive nephropathy (CPN). In some 500 mg/kg/day females, the constellation of lesions diagnosed as CPN may be more representative of retrograde nephropathy, rather than typical CPN. Statistically significantly increased incidences of hyperplasia of squamous epithelium were observed in the nonglandular stomach (limiting ridge

only) and the tongue in females at 500 mg/kg/day. In the tongue, subacute/chronic inflammation occurred in association with squamous epithelial cell hyperplasia.

Test article-related neoplastic changes occurred in the liver of females administered 500 mg/kg/day, and consisted of an increased incidence of hepatocellular adenoma and hepatocellular carcinoma. The increased incidences of hepatocellular tumors occurred in association with degenerative/necrotic changes in the liver at this dose level (see above under discussion of non-neoplastic lesions). No hepatocellular tumors and no test article-related degenerative or necrotic changes were observed in lower dose females and the incidence of hepatocellular tumors in males was comparable between the controls and the 50 mg/kg/day group.

Equivocal increases in pancreatic acinar cell tumors and testicular interstitial (Leydig) cell tumors occurred in males administered 50 mg/kg/day. In males at 50 mg/kg/day, a statistically significant increase was observed in the incidence of pancreatic acinar cell adenoma/carcinoma combined, but not adenoma or carcinoma alone. In addition, the incidences of acinar cell hyperplasia were not significantly different from controls in any of the treated male groups. However, based on the known PPARα agonist activity of the test article, the marginal increase in pancreatic acinar cell tumors in the 50 mg/kg/day male group provides equivocal evidence of a test article-related effect.

The incidence of interstitial cell adenoma of the testes was increased in males at 50 mg/kg/day, and one interstitial cell adenoma was also present in one male in the 50 mg/kg/day group at the interim necropsy. The incidence of interstitial cell hyperplasia at 50 mg/kg/day was also higher than in control males. Since PPARα agonists are known to produce proliferative interstitial cell lesions (hyperplasia and adenoma) in the testes of rats, a relationship to treatment for these findings in the 50 mg/kg/day male group cannot be ruled out. However, based on the marginal nature of the increased incidences of these lesions, their lack of statistical significance, and the relatively high incidence of these lesions in concurrent controls, the relationship to treatment for these findings is equivocal. The incidences of proliferative interstitial cell lesions of the testes in the 0.1 and 1 mg/kg/day groups, were similar to or less than controls.

No adverse pathology findings occurred in male rats administered 0.1 or 1 mg/kg/day or in females administered 1 or 50 mg/kg/day.

Under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for chronic toxicity of was 1 mg/kg/day in male rats and 50 mg/kg/day in females. The NOAEL in males is based on increases in focal cystic degeneration, focal necrosis, and centrilobular necrosis of the liver, with associated increases in cytotoxic liver enzymes, and equivocal increases in pancreatic acinar cell tumors and testicular interstitial (Leydig) cell tumors, all observed at 50 mg/kg/day. In females the NOAEL is based on reductions in body weight, body weight gain, and food efficiency; mild decreases in red cell mass; increases in individual cell necrosis in the liver, hyperplasia and/or inflammation in the nonglandular stomach and tongue; an increase in incidence and severity of microscopic pathology in the kidneys; and an increase in hepatocellular adenomas and carcinomas, all observed at 500 mg/kg/day.

Test article-related increases in hepatocellular adenoma and hepatocellular carcinoma were observed in females at 500 mg/kg/day. Equivocal increases in pancreatic acinar cell tumors and testicular interstitial (Leydig) cell tumors occurred in males administered 50 mg/kg/day. Clear thresholds were established for all of these tumor types, as test article-related tumor responses occurred only at the highest doses tested in males and females. Most research indicates that induction of these specific tumors in rats by non-genotoxic peroxisome proliferators likely has little or no relevance in humans, especially in plausible human exposure scenarios.

2. INTRODUCTION

This study was conducted in accordance with Standard Operating Procedures (SOPs) and the protocol as approved by the Sponsor. SOP and protocol deviations were acknowledged by the Study Director and documented in the raw data. In the opinion of the Study Director, none of the SOP deviations were considered to have affected the quality or integrity of the study. This study was based on United States Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Guideline 870.4300, Combined chronic toxicity/carcinogenicity, August 1998. The experimental design and methods were also based on the Organization for Economic Cooperation and Development (OECD) Guideline 453, September 2009, the Japanese Ministry of Agriculture, Forestry and Fisheries Guidelines for Data Requirements for Supporting Registration of Pesticides, No. 12-Nousan-8147, Notification by Director-General dated 24 November, 2000, and the Commission Directive 88/302/EEC B.33 Combined Chronic/Carcinogenicity test, *Methods for the Determination of Toxicity* (1988). The protocol and amendments are presented in Appendix M. Procedures pertinent to this study are described in this report.

2.1. Objective

The objective of this study was to evaluate the potential chronic toxicity and oncogenicity of when administered via oral gavage over the major portion of the life span of the test animals.

2.2. Species Selection

The current state of scientific knowledge and the applicable guidelines cited previously did not provide acceptable alternatives, *in vitro* or otherwise, to the use of live animals to accomplish the purpose of this study. "The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires *in vivo* experimentation with a wide variety of animal species."[1] "Whole animals are essential in research and testing because they best reflect the dynamic interactions between the various cells, tissues, and organs comprising the human body."[2]

The rat is a frequently used model for evaluating the toxicity of various classes of chemicals and for which there is a large historical database.

2.3. Justification for Number on Study

This study was designed to use the fewest number of animals possible, consistent with the objective of the study, the scientific needs of the Sponsor, contemporary scientific standards, and in consideration of applicable regulatory requirements cited previously. This study was designed to use the smallest number of animals possible that allowed sufficient group sizes for meaningful statistical analysis of data.

2.4. Study Schedule

Protocol Approved by Sponsor	July 12, 2010
Study Initiation Date (Protocol Signed by Study Director)	July 12, 2010
Experimental Starting Date (Receipt of Test System)	July 15, 2010
Experimental Start Date (First Day of Dosing)	July 29, 2010
Termination Date (Last Day Animals Were on Study)	July 20, 2012
Experimental Completion Date (Final Data Collection)	March 25, 2013
Draft Report Mail Date	February 25, 2013

3. MATERIALS AND METHODS

3.1. Vehicle and Test Article Information

Pertinent vehicle and test article receipt information is presented in Appendix A.

Documentation of the strength/purity, composition, stability, and other pertinent information for the lot of vehicle used on study was limited to that information listed on the label and accompanying documentation of this commercially available product.

The Sponsor has provided documentation of the strength/purity, composition, stability, and other pertinent information for the lot of test article used on study.

3.1.1. Vehicle and Test Article Preparation

Fresh vehicle, deionized water, was dispensed for use on study weekly and was stored at room temperature.

The test article, was used as received from the Sponsor. The test article formulations were adjusted for purity of 84%. The test article was mixed with the appropriate amount of deionized water to achieve the desired concentrations. Formulations of the test article were prepared weekly at nominal concentrations of 0.01, 0.1, 5, and 50 mg/mL, and were stored at room temperature.

3.1.2. Analysis of Dosing Formulations

Dosing formulations prepared for the study were evaluated for homogeneity and concentration. Appropriate samples (see following table) were collected, while stirring, using a positive displacement pipette or syringe and placed into 15 mL amber glass bottles. Following acceptance of the analytical results (signing of the final report) by the Study Director, or at the discretion of the Study Director, backup samples will be discarded.

Dosing Formulation Analysis Sample Collection							
	Dose Level Sampled		Number of Samples per Concentration			Sample Volume	Intervals
Sample Type	(mg/kg/day)	Stratum	Collected	Analyzed	Backup	(mL)	(Weeks)
Homogeneity Analyses[a]	0.1, 1, 50, and 500	Top	6	2	4	1	1 and 44[b]
		Middle	6	2	4	1	
		Bottom	6	2	4	1	
Concentration Analyses[a]	0, 0.1, 1, 50, and 500	Middle	6	2	4	1	1, 2, 3, 4, 17, 30, 47, 48, 56, 69, 82, and 95

[a]The samples, including backup samples, were stored frozen at -10 to -30°C pending analyses or final disposition.
[b]Duplicate samples from the top, middle, and bottom stratum at the 0.1 mg/kg/day dose level were also analyzed.

Stability for the concentration range used in this study was established under for 14 days at room temperature.

3.1.2.1. Analyses

Samples were stored frozen at -10 to -30° until shipped on dry ice to the site at , for analysis. All analytical work was conducted by using an analytical method developed and validated by
Analytical method deviations occurred and are documented in study records and the analytical report (Appendix B). However, none were considered to invalidate the method and the method was considered to be adequate for analysis of dosing formulations.

3.1.3. Reserve Sample and Test Article Disposition

A reserve sample from the lot of test article used in this study was collected and stored at in a secure area with the appropriate environmental controls. Any remaining test article will be shipped to the Sponsor after completion of the study.

3.2. Experimental Design

3.2.1. Animal Acquisition and Acclimation

A total of 400 male and 400 female CD® [Crl:CD(SD)] rats (approximately 5 weeks of age at receipt) were received from Charles River Laboratories, Portage, Michigan, on July 15, 2010. During the 14 day acclimation period, the animals were observed daily with respect to general health and any signs of disease. The animals were administered a sham dose of tap water on two occasions in the same manner and volume intended for use during the study period.

3.2.2. Randomization, Assignment to Study, and Maintenance

Using a standard, by weight, measured value randomization procedure, 345 male and 345 female animals (weighing 131 to 154 g and 97 to 128 g, respectively, at randomization) were assigned to the control and treatment groups identified in the following table.

Group Assignments

Group Number	Dose Level (mg/kg/day)	Number of Animals[a]	
		Male	Female
1	0	80	80
2	0.1	80	-
3	1	80	80
4	50	80	80
5	500	-	80
Sentinels			
89	-	25	25

[a]Ten animals/sex/group were designated for the 12 month interim necropsy. The remaining surviving animals were designated for the terminal necropsy.

Animals assigned to study had body weights within ±20% of the mean body weight for each sex. Extra animals obtained for the study, but not placed on study, were euthanized via carbon dioxide inhalation. Euthanasia was confirmed via cervical dislocation and the carcasses were discarded.

Each animal was assigned an animal number to be used in the Provantis™ data collection system and was implanted with a microchip bearing a unique identification number. The individual animal number, implant number, and study number comprised a unique identification for each animal. Each cage was identified by the animal number, study number, group number, and sex.

Animals found dead or euthanized *in extremis* during the first 17 days of the study were replaced. A total of four CD® [Crl:CD(SD)] rats were utilized as replacement animals and were assigned a unique animal number. The data recorded for the replaced animals are not reported but are maintained in the study file.

The animals were pair-housed (same-sex) in polyboxes with non-aromatic bedding in an environmentally controlled room. Animal enrichment was provided according to SOP. Fluorescent lighting was provided for approximately 12 hours per day. The dark cycle was interrupted intermittently due to study-related activities. Temperature and humidity were continuously monitored, recorded, and maintained to the maximum extent possible within the protocol-designated ranges of 64 to 79°F and 30 to 70%, respectively. The actual temperature and humidity findings are not reported but are maintained in the study file.

Block Lab Diet® (Certified Rodent Diet #5002, PMI Nutrition International, Inc.) was available *ad libitum,* except during designated periods. The lot number from each diet lot used for this study was recorded. Certification analysis of each diet lot was performed by the manufacturer. Tap water was available *ad libitum* via an automatic watering system. The water supply is monitored for specified contaminants at periodic intervals according to SOP. The results of food and water analyses are retained in the Archives. The Study Director is not aware of any potential contaminants likely to be present in the diet or water that would have interfered with the results of the study. Therefore, no analyses other than those stated above were conducted.

3.2.3. Test Article Administration

3.2.3.1. Justification for Route of Administration and Dose Selection

The oral gavage route was selected as the most efficient way to administer an accurate dose.

In a previous study ( ), Crl:CD(SD) rats (10/sex/dose) were dosed with the test substance by oral gavage for at least 90 days at daily doses of 0, 0.1, 10, or 100 mg/kg/day for males and 0, 10, 100, or 1000 mg/kg/day for females. In the 1000 mg/kg/day group, three females died prior to scheduled sacrifice and others displayed clinical signs. No other test substance-related effects were observed in surviving animals in all groups on body weight or nutritional parameters, clinical or ophthalmological observations, or neurobehavioral parameters.

Test substance-related findings included regenerative anemia (males: 100 mg/kg/day; females: 1000 mg/kg/day), clinical chemistry effects consistent with PPARα activation (males: ≥10 mg/kg/day; females: 100-1000 mg/kg/day), and increased liver weights and associated hepatocellular hypertrophy (males: ≥10 mg/kg/day; females: 1000 mg/kg/day). Similar liver effects were observed at >3 mg/kg/day in males and 300 mg/kg/day in females in a rat 28-day gavage study ( ). Increased kidney weights were observed in males and females at ≥10 mg/kg/day. In females, renal papillary necrosis and/or renal tubular necrosis were observed in the two females found dead prior to scheduled sacrifice and in one female that survived to the scheduled sacrifice. Clinical and anatomic pathology parameters were fully or partially (male hematology effects; liver weights) reversible after an approximate 4-week recovery period.

Based on the results of the 90-day and 28-day studies, doses selected for this study were 0, 0.1, 1, and 50 mg/kg/day in males and 0, 1, 50, and 500 mg/kg/day in females. The high dose was expected to produce effects on clinical chemistry and liver weight and microscopic pathology in males and females, without producing excessive liver toxicity. The middle dose was expected to possibly produce liver and clinical chemistry effects in either sex or to be a no-observed-adverse-effect level (NOAEL). The low dose was expected to be a NOAEL in both males and females.

3.2.3.2. Administration

The vehicle and test article were administered once daily for up to 104 weeks in males and up to 101 weeks in females during the study via oral gavage. The dose levels were 0.1, 1, and 50 mg/kg/day for males and 1, 50, and 500 mg/kg/day for females and administered at a dose volume of 10 mL/kg/dose. The control group received the vehicle in the same manner as the treated groups. Individual doses were based on the most recent body weights. Based on

analytical results, male rats in the low dose group (0.1 mg/kg/day) received approximately double the nominal dose during Week 44. This was not considered to have impacted the study results as this dose was below the NOAEL and no adverse effects were observed in this group during that week.

3.3. In-life Examinations

3.3.1. Cageside Observations

All animals were observed for morbidity, mortality, injury, and the availability of food and water twice daily. The afternoon cageside observation was conducted at approximately the same time each day (±2 hours). Beginning at Week 53, a third cageside observation was conducted daily in the evening. On occasion, veterinary consultations were conducted during the course of the study. All treatments and observations were recorded. The medical treatments and observations are not reported but are maintained in the study file.

3.3.2. Detailed Clinical Observations

A detailed clinical examination of each animal was performed prior to randomization and weekly during the study. The examinations performed prior to randomization are not reported but are maintained in the study file. On occasion, clinical observations were recorded at unscheduled intervals. The observations included, but were not limited to, evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, and nervous system effects including tremors, convulsions, reactivity to handling, and bizarre behavior, and the palpation of masses. The location, appearance, and size of the masses were documented.

3.3.3. Body Weights

Body weights for all animals were measured and recorded the day after receipt, prior to randomization (Week -2), weekly for the first 14 weeks starting on Day 1 (prior to dosing), and every other week thereafter during the study. The body weights recorded the day after receipt, prior to randomization, and for sentinel animals are not reported but are maintained in the study file. Body weight change was calculated and reported weekly, for the first quarter (Weeks 1 to 13), the first year (Weeks 1 to 52), and for the entire study (Weeks 1 to 104 for males and Weeks 1-100 for females).

3.3.4. Food Consumption and Food Efficiency

Food consumption was measured and recorded pretest (Week -1), weekly during the first 13 weeks, and for 2 week intervals starting on Week 14 during the study. The food consumption was measured for the cage and divided by the number of surviving animals. Food consumption and food efficiency was calculated weekly, the first quarter (Weeks 1 to 13), the first year (Weeks 1 to 52), and for the entire study (Weeks 1 to 102 for males and Weeks 1 to 100 for females).

3.3.5. Ophthalmoscopic Examinations

Ophthalmoscopic examinations were conducted on all animals pretest and on all surviving animals prior to the interim and terminal necropsies by
The pretest eye exams conducted on sentinel animals are not reported but are maintained in the study file.

3.3.6. Serological Health Screen

Serological health screen tests were conducted pretest and at 6, 12, and 18 months on three to five sentinel animals/sex and at 24 months on three female sentinel animals, based on survival. Serological evidence of the following was determined:

Pretest and at 12 and 24 months

- Pneumonia Virus
- Reovirus Type 3
- Theiler's Encephalomyelitis Virus (GD-7)
- Sendai Virus
- Lymphocytic Choriomeningitis Virus
- Kilham Rat Virus
- Rat Coronavirus/Sialodacryoadenitis Virus
- Toolan's H-1 Virus
- Rat Parvovirus
- *Mycoplasma Pulmonis*

At 6 and 18 months

- Sendai Virus
- Kilham Rat Virus
- Rat Coronavirus/Sialodacryoadenitis Virus
- Toolan's H-1 Virus
- Rat Parvovirus
- *Mycoplasma Pulmonis*

Blood (1 to 2 mL) for the viral screens was collected via the vena cava after carbon dioxide inhalation. The blood was processed to serum and two approximately equal aliquots were obtained. The serum samples were stored frozen at -10 to -30°C.

Necropsy examinations were performed on each animal after blood collection. Following necropsy, the carcasses were discarded and no tissues were saved.

3.3.7. Clinical Pathology

Clinical pathology evaluations were conducted on 10 animals/sex/group at 3, 6, and 12 months (hematology and clinical chemistry) and 10 animals/sex/group at 6 and 12 months (coagulation and urinalysis). The animals had access to drinking water but were fasted overnight prior to scheduled sample collection. Blood samples (approximately 2.8 to 4 mL) were collected via the

vena cava or cardiac puncture after carbon dioxide inhalation. The samples were collected into tubes containing K_3EDTA for evaluation of hematology parameters, sodium citrate for evaluation of coagulation parameters, and serum separators with no anticoagulant for the clinical chemistry samples. The order of bleeding was by alternating one animal from each dose group, then repeating to reduce handling and time biases. On occasion, blood samples were redrawn. Animals were not fasted prior to these additional collections.

The animals were housed in stainless steel metabolism cages and urine was collected for at least 12 hours.

Blood samples (0.5 mL) for peripheral blood smears were conducted on all surviving animals at 12 and 18 months and prior to terminal necropsy. The animals designated for a full clinical pathology collection had access to drinking water but were fasted overnight prior to scheduled sample collection. The animals designated for only blood smear samples had access to drinking water and food prior to sample collection.

3.3.7.1. Hematology Parameters Evaluated

- leukocyte count (total and absolute differential)
- erythrocyte count
- hemoglobin
- hematocrit
- mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration (calculated)
- absolute reticulocytes
- platelet count
- blood cell morphology

3.3.7.2. Coagulation Parameters Evaluated

- prothrombin time
- activated partial thromboplastin time

3.3.7.3. Clinical Chemistry Parameters Evaluated

- alanine aminotransferase
- alkaline phosphatase
- sorbitol dehydrogenase
- total protein
- albumin
- globulin and A/G (albumin/globulin) ratio (calculated)
- urea nitrogen
- creatinine
- total cholesterol
- triglycerides

- total bilirubin (with direct bilirubin if total bilirubin exceeds 1 mg/dl)
- aspartate aminotransferase
- total bile acids
- glucose
- calcium
- phosphorus
- electrolytes (sodium, potassium, and chloride)
- gamma glutamyl transferase

3.3.7.4. Urinalysis Parameters Evaluated

- volume
- specific gravity
- pH
- color and appearance
- protein
- glucose
- bilirubin
- ketones
- blood
- urobilinogen
- microscopy of centrifuged sediment

3.4. Postmortem Study Evaluations

Postmortem study evaluations were performed on animals euthanized *in extremis*, animals found dead, and on all surviving animals at the scheduled interim (12 month) and terminal (24 months) necropsies. The methods are described in Appendix K.

3.5. Statistics

The table below defines the set of comparisons used in the statistical analyses described in this section.

Table of Statistical Comparisons	
Control Group	Treatment Groups
1	2 (males only), 3, 4, 5 (females only)

The raw data were tabulated within each time interval, and the mean and standard deviation were calculated for each endpoint by sex and group. For each endpoint, treatment groups were compared to the control group using the analysis outlined below. Data for some endpoints, as indicated, were transformed by either a log or rank transformation prior to conducting the specified analysis.

Statistical Analysis	
Endpoints	Type of Analysis
Body Weight Body Weight Gain Food Consumption Hematology (except leukocyte counts) Coagulation Clinical Chemistry Organ Weights Absolute Weights Relative to Body and Brain Weights	Group Pair-wise Comparisons
Leukocyte Counts Total Leukocyte Counts Differential Leukocyte Counts	Log Transformation Group Pair-wise Comparisons (Levene's/ANOVA-Dunnett's/Welch's)
Urinalysis Urine Volume Specific Gravity pH Food Efficiency	Rank Transformation with Dunnett's Test
Mortality Data	Survival Analysis
Tumor Data	Tumor Analysis
Non-Tumor Microscopic Pathology Data	Tumor Analysis

3.5.1. Group Pair-Wise Comparisons (Levene's/ANOVA-Dunnett's/Welch's)

If sample sizes for all groups were three or greater, Levene's test[3] was used to assess homogeneity of group variances for each specified endpoint and for all collection intervals. If Levene's test was not significant ($p \geq 0.01$), a pooled estimate of the variance (Mean Square Error or MSE) was computed from a one-way analysis of variance (ANOVA) and utilized by a Dunnett's[4] comparison of each treatment group with the control group. If Levene's test was significant ($p < 0.01$), comparisons with the control group were made using Welch's t-test[5] with a Bonferroni correction.

In the case that sample size was less than three for at least one treatment group, Levene's method could not be implemented. Groups with sample sizes less than three were excluded from the analysis and control-treatment pair-wise comparisons that satisfied the sample size assumption ($n \geq 3$) were conducted using Welch's t-test with a Bonferroni correction.

If there were only two groups involved, the above methodology applied and the Dunnett's test reduced to a Student's t-test.[6]

Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

3.5.2. Log Transformation with Group Pair-wise Comparisons

Historical data indicates that leukocyte counts (total and differential) are not normally distributed; therefore, a log transformation was performed on these data. The transformed data were then analyzed as described in the Group Pair-wise Comparisons section.

3.5.3. Rank Transformation with Dunnett's Test

Historical data indicate that certain urinalysis endpoints and the food efficiency endpoint have unpredictable distribution characteristics, thus analysis was enhanced by use of a non-parametric test. For each specified endpoint (see table above) and for each collection interval, a rank transformation was performed. The transformed data was then analyzed using Dunnett's test, to compare each treatment group with the control group.

If sample size for the control group was two or greater, Dunnett's test was used to compare each treatment group having a non-zero sample size with the control group.

If there were only two groups involved, the above methodology applied and the Dunnett's test reduced to a Student's t-test. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

3.5.4. Survival Analysis

Intercurrent mortality data were analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using a log-rank test.[7] If this overall test was significant ($p<0.05$) and there were more than two groups, then a follow up analysis was done where each treatment group was compared to the control group using a log-rank test.

Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed.

3.5.5. Tumor Analysis

Tumor incidence data were analyzed using both survival adjusted and unadjusted tests. The unadjusted tests were based on the incidence and number of sites examined for each tumor type. The Cochran-Armitage trend test[8] was calculated and Fisher's exact test[9] was used to compare each treatment group with the control group. The survival adjusted test was conducted according to the prevalence/mortality methods described by Peto et al.[10] Evaluation criteria (p-values of significance) were applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%).[11] The evaluation criteria are given in the following table.

Evaluation Criteria for Common and Rare Tumors	
Test for Positive Trends	**Control-High Pair-wise Comparisons**
Common and rare tumors were tested at the 0.05 significance level.	Common and rare tumors were tested at the 0.05 significance level.

Electronic data will be provided for this study with the final report. The format of the data sets will be prepared following the guidelines of the United States Environmental Protection Agency (EPA).

3.6. Computer Systems

The computer systems used during the conduct of this study are presented in Appendix L.

3.7. Data and Specimen Retention

All raw data, documentation, records, protocol, reserve samples, specimens, and the final report generated as a result of this study will be retained at , or an approved archive facility contracted by for a period of 1 year following issuance of the draft report. Retention of materials after the time stated above is subject to a future contractual agreement. The tissue slides sent for pathology peer review to the Sponsor will be archived at that site.

4. RESULTS AND DISCUSSION

4.1. Analysis of Dosing Formulations

The Formulation Analysis Report (including the Analytical Method and individual results of the dosing formulations for concentration and homogeneity and Quality Assurance Statement) is presented in Appendix B.

4.1.1. Homogeneity

The dosing formulations prepared for Week 1 at each concentration were evaluated for homogeneity. Samples from the top, middle, and bottom were collected from each dosing group. The results showed all concentrations met the homogeneity acceptance criteria (100 ±10% average recovery; ≤5% RSD). The average concentrations of the homogeneity samples ranged from 93.2 to 95.3 of nominal with a RSD of 0.710 to 1.98%.

4.1.2. Concentration

A summary of the concentration analysis of in dosing formulations is presented in Table 5. Weeks 1, 2, 3, 4, 17, 30, 44, 47, 48, 56, 69, 82, and 95 dose formulations were analyzed for concentration verification. Duplicate samples from the middle stratum at the 0.0 mg/mL (vehicle control), 0.01 mg/mL, 0.1 mg/mL, 5.0 mg/mL, and 50 mg/mL concentration were injected and analyzed. Duplicate samples from the top, middle, bottom stratum at the 0.01 mg/mL concentration from the Week 44 dosing formulations were also injected and analyzed. Samples for each level met the sample analysis acceptance criteria for accuracy and precision (100 ±10% average recovery; ≤5% RSD through Week 48, ≤10% RSD from Week 48 through the end of the study), with a few exceptions. Most of the deviations from acceptability criteria were small and were not considered to have impacted the study. See analytical report Appendix B for details.

The Week 44 samples (original and backup samples) of the 0.01 mg/mL formulation were approximately double the nominal concentration. These values support that animals in this (male only) group received approximately double the nominal dose of test substance during that week. This deviation did not impact the overall integrity of the study as this dose was below the NOAEL for males, and no adverse effects were observed that were attributed exposure to this higher than nominal dose.

4.1.3. Analytical Conclusion

All system suitability test (SST), performance check, and calibration standards met the sample analysis acceptance criteria. Dose formulation samples were analyzed for homogeneity and concentration verification. All samples met the sample analysis acceptance criteria for accuracy and precision (average concentration within ±10% recovery of the nominal concentration, ≤5% RSD through Week 48, ≤10% RSD from Week 48 through the end of the study), with a few exceptions. Most of these deviations were minor and were considered not to have impacted the study. The concentration of the 0.01 mg/mL formulation was demonstrated to be approximately double the nominal concentration during week 44. This was not considered to have impacted the integrity of the study as this was below the NOAEL for males, and no adverse effects were

observed in the animals that received this formulation. In addition, test article was not detected in the vehicle control samples.

4.2. In-life Examinations

4.2.1. Mortality and Cause of Death

Mean survival data are illustrated in Figure 1 and summarized in Table 1. A record of fate and disposition is presented in Appendix C.

There were no test article-related effects on survival over the course of this study. Numerous deaths occurred and these incidences are included in Appendix C. A single test article-related cause of death/moribundity was inflammation/necrosis of the kidneys which occurred in seven of the 500 mg/kg/day females and was characterized by papillary necrosis. In males the most common causes of death/moribundity were pituitary tumors and undetermined. In females the most common causes of death/moribundity were mammary tumor and pituitary tumor. Females were terminated during Week 101, prior to scheduled termination, due to low survival in all female dose groups, especially control and 50 mg/kg/day groups. However, this did not impact the study as this was approximately 2 years of test article exposure. Even though, survival among all female groups was low there were no statistically significant differences and survival was comparable among all groups.

4.2.2. Detailed Clinical Observations and Mass Findings

Detailed clinical observations and mass findings (identified as part of clinical observations) are summarized in Tables 2 and 3, respectively. Individual detailed clinical observations and individual mass findings are presented in Appendices D and E, respectively.

There were no test article-related clinical observations. All observations were transient or common in these species and were not considered test article-related.

There was no test-article related increase in masses or mass findings.

4.2.3. Body Weights and Body Weight Change

Body weight data are illustrated in Figure 2 and summarized in Table 4. Body weight change values are summarized in Table 5. Individual body weight values are presented in Appendix F.

Exposure to the test substance produced no adverse reductions in body weight and body weight gain in males. Mean body weight in 50 mg/kg/day males was statistically significantly below control over most of the first year, although mean body weight was only 4% below control in males at Week 52 (not statistically significant), and exceeded the control value at termination. Mean body weight gain in this group was 6% below control in males over Weeks 1 to 52 and exceeded the control value over the two year period. Based on the small magnitude of the changes, the effect among males at 50 mg/kg/day was not considered adverse.

Exposure to 500 mg/kg/day of the test substance produced adverse reductions in body weight and body weight gain in females. In this group, statistically significantly lower mean body

weight was observed from weeks 30 through 86. Mean body weight was 13% below control at Week 52, and mean body weight gain was 20% below controls over Weeks 1 to 52 (both statistically significant). Mean final body weight (week 100) and overall body weight gain (Weeks 1-100) were comparable to the control value. However, these body weight changes were considered adverse at this dose based on the difference during the first year on study.

No adverse effects on body weight were observed in any other dose group. Mean body weight and body weight gain was lower in females at 1 mg/kg/day over most of the first year of the study. This finding was not considered test article-related as no dose response was noted, the small magnitude of the difference, and the fact that it did not persist over the remainder of the study. Statistically significant differences in body weight or body weight gain were observed in all dose groups during weekly/biweekly measurements, but were not attributed to test article exposure as they were intermittent, included both higher and lower values (relative to control), and did not demonstrate a consistent dose-response.

4.2.4. Food Consumption and Food Efficiency

Food consumption data are illustrated in Figure 3 and summarized in Table 6. Individual food consumption values are presented in Appendix G. Food efficiency values are summarized in Table 7.

There were no adverse test article-related effects on food consumption in either sex or in food efficiency in males at any dose. Adverse effects on food efficiency were observed in 500 mg/kg/day females. In this group, food efficiency was 23% below control (statistically significant) over the first year and 11% below control (statistically significant) overall (Weeks 1-100).

Lower mean food efficiency was noted over the first year in males at 50 mg/kg/day. However, overall (Weeks 1-104) food efficiency was comparable to controls. No effects were noted in any other dose group. A few statistically significant differences in food consumption or food efficiency were observed in all dose groups during weekly/biweekly measurements, but were not attributed to test article exposure as they were intermittent and did not demonstrate a consistent temporal- or dose-response.

4.2.5. Ophthalmoscopic Examinations

Ophthalmoscopic examination data and interpretation are presented in Table 8 and Appendix H.

No test article-related findings were noted in the interim or terminal ophthalmoscopic examination.

4.2.6. Clinical Pathology

The Clinical Pathology Report is presented in Appendix J.

4.2.6.1. Hematology

At the 3, 6, and 12 month intervals there were mild decreases in red cell mass (erythrocytes, hemoglobin, and hematocrit in females receiving 500 mg/kg/day. Effects were mild in females (up to 28% less than control) and were not associated with any test article-related effects on erythrocyte morphology. Appropriate increases in reticulocytes (106% above respective) occurred in response to the decreases in red cell mass. The increases in reticulocytes were associated with expected decreases in MCHC and increases MCV. This collection of findings is suggestive of red cell loss or hemolysis although the exact mechanisms involved are unknown. All of these findings were considered test article-related and adverse.

Statistically significant decreases in red cell mass were also present in males receiving 50 mg/kg/day at the 3- and 6-month interval. However, the decreases were small (decreases were less than 10% from control except for hemoglobin at 3 months) and did not induce statistically significant changes in reticulocytes. In addition, red mass changes were transient—at the 12 month interval there were no statistically significant changes in any red cell mass parameter, and values in individual animals in the 50 mg/kg/day group were similar to controls. Therefore, the red cell mass changes in 50 mg/kg/day males were considered to be test article-related but nonadverse.

All other mean and individual hematology values were considered to be within an acceptable range for biologic and procedure-related variation. These include the following:

- Group mean erythrocytes were statistically lower in the 50 mg/kg/day female group at 12 months. This finding was considered unrelated to treatment, as the difference relative to control was small (6%), there were no statistically significant changes in hemoglobin or hematocrit in this group at this time point, and there were no statistically significant changes in any red cell mass parameter in this group at the 3- and 6-month time point.

- Statistically lower hemoglobin in the 1 mg/kg/day female groups at 3 months did not occur in a dose-related manner, was not associated with statistically significant changes in other red cell mass parameters at any time point, and was thus also considered a spurious finding.

4.2.6.2. Peripheral Blood Smear Leukocyte Differential Counts

No test article-related effects among leukocytes were observed in either sex at any interval (12, 18 and 24 months) in which these evaluations were performed.

4.2.6.3. Coagulation

There were no test article-related effects among coagulation times in either sex at any dose level. All mean and individual values were considered within an acceptable range for biologic and/or

procedure-related variation. Statistically decreased APTT was present in the 500 mg/kg/day female group at the 12-month time point. These changes were not considered toxicologically significant based on the direction of change (decreased rather than prolonged) and absence of correlative findings in other coagulation parameters.

4.2.6.4. Clinical Chemistry

Liver Enzymes

At the 12-month interval in males receiving 50 mg/kg/day, there were mild increases relative to controls in enzymes indicative of liver injury including alkaline phosphatase, ALT, AST and sorbitol dehydrogenase (sorbitol dehydrogenase and AST not statistically significant). These enzyme changes correlated with microscopic findings of minimal cystic degeneration and minimal to mild focal necrosis in the liver of males at 50 mg/kg/day. Therefore, these enzymes changes were considered test article-related and adverse.

Minimal but statistically significant increases in alkaline phosphatase were also present at the 3- and 6-month intervals in the 50 mg/kg/day male group. At these intervals, increases in alkaline phosphatase were less than those present at 12 months and were not associated with statistically significant changes in other enzymes indicative of hepatic or hepatobiliary injury. Therefore, the changes in alkaline phosphatase in the 50 mg/kg/day male group at the 3 and 6 month intervals may be due in part or in whole to test article-related enzyme induction, as the test article was previously shown to produce an increase in total P450 enzyme activity in male rats at 30 mg/kg/day (Haas, 2008).[12]

There were no test article-related changes in liver enzymes in males receiving 1 or 0.1 mg/kg/day or in females at any of the dose levels tested (up to 500 mg/kg/day).

Serum Proteins

Minimal, statistically significant increases in albumin were present in males receiving 50 mg/kg/day at all intervals (up to 16% above controls) and in females receiving 500 mg/kg/day at the 3-month interval (10% above controls). In addition, statistically significant decreases (of up to 17% below control) in globulin were present in females at 500 mg/kg/day at all intervals (an associated decrease in total protein was also present in this group at the 6-month interval). No statistically significant decreases in globulin were present in males at any dose or interval, small decreases in individual values for these parameters in individual animals in the 50 mg/kg/day male group may have been test article-related. The changes in albumin and globulin in the high-dose male and female groups also resulted in statistically significant increases in albumin/globulin ratio in these groups at all intervals.

The test article is a peroxisome proliferator , 2008)[12], and the pattern of change in serum proteins observed in high dose males and females-lower globulin and higher albumin-is a well-established response to PPARα activation. Peroxisome proliferators are anti-inflammatory, producing decreases in acute phase proteins (which contribute to the globulin fraction), and increases in negative acute phase protein (albumin) (Gervois et al., 2004).[13] However, no adverse biological outcomes have been associated with such changes in these serum proteins.

Therefore, these changes in serum proteins in high dose males and females were considered test article-related although they were not considered biologically relevant based on their small magnitude and lack of association with known adverse outcomes.

In addition to the serum protein changes noted above, minimal, statistically significant increases in albumin/globulin ratio were present in the 1 mg/kg/day males and 50 mg/kg/day females at all intervals. Also, in some individual animals in these groups, albumin tended to be higher and globulin lower than controls. However, group mean albumin and globulin in these groups were not statistically different from controls (with the exception of elevated albumin in the 1 mg/kg/day male group at 12 months and decreased globulin in the 50 mg/kg/day female group at 6 months), and differences from control group means for both albumin and globulin were ≤ 8% at all intervals. Therefore, the statistically significant changes in albumin/globulin ratio in these groups were also considered to be test article-related but nonadverse based on the minimal nature of the changes.

Other

All other mean and individual clinical chemistry values were considered within an acceptable range for biologic and procedure-related variation. There were other statistically significant changes among clinical chemistry analytes that were not considered of any additional relevance to the test article based on their small magnitude, sporadic nature, direction of change, relation to changes already discussed, and/or lack of a dose response. These are discussed in more detail below.

- Phosphorus was statistically higher than control in the 500 mg/kg/day female group at the 12-month interval. The relationship to treatment for this difference is uncertain; however values in individual rats in this group were similar to controls except for one animal, and there were no statistically significant changes in phosphorus in any treated group at any other time point. Therefore, based on the minimal nature of these changes, they were not considered to be adverse.

- Phosphorus was also statistically higher in the 0.1 and 50 mg/kg male groups at the 3-month interval. These differences were considered to be unrelated to test article administration since they did not occur in a dose-related manner and there were no statistically significant differences in phosphorus in any treated group relative to control at the 6- and 12- month intervals.

- Calcium was statistically higher in the 50 mg/kg/day males at the 12-month interval. One fraction of serum calcium exists as “bound” to albumin, and increases in albumin are necessarily associated with physiologically appropriate increases in calcium. Changes in bound calcium have no effect on unbound (“ionized”) calcium, which is the physiologically active form of calcium. Therefore, the increase in calcium in the 50 mg/kg/day male group at 12 months was considered to be secondary to albumin changes, physiologically irrelevant, and thus non-adverse.

- Urea nitrogen was statistically higher than the respective control in the 1 mg/kg/day male group at the 12-month interval and in the 50 mg/kg/day male group at the 6-month interval. These differences were not dose-related and/or were not consistent across time, and there were no correlative changes in related clinical chemistry parameters or with microscopic changes in the kidneys. Therefore, these differences were considered spurious and unrelated to administration of the test article.

- Chloride was statistically higher than control in females at 1 and 500 mg/kg/day (but not at 50 mg/kg/day) at the 6-month interval. These differences were not considered to be test article-related as they very slight (only 2% above control), did not occur in a dose-related manner, and were not associated with changes in chloride at any other interval.

4.2.6.5. Urinalysis

In females receiving 500 mg/kg/day, minimal, statistically significant increases in urine volume and decreases in urine specific gravity-suggestive of a minimal diuresis-were present at both the 6- and 12-month intervals. Although minimal and not associated with changes in kidney-related chemistry parameters (e.g., urea nitrogen, creatinine), these changes may be correlative to increased incidences and severity of chronic progressive nephropathy observed microscopically in this dose group at the 1-year interim sacrifice.

Urine pH was increased in males at all dose levels and in females receiving 1 or 500 mg/kg/day. These changes in urine pH are of uncertain relationship to administration of the test article based on the lack of a clear dose response across the affected groups. However, based on the lack of any correlative findings suggestive of an effect on the urogenital system (except in the kidneys of the 500 mg/kg/day females, as noted above), the changes in urine pH were considered nonadverse.

All other individual urinalysis values were considered within an acceptable range for biologic and procedure-related variation.

4.2.7. Serological Health Screen

Individual serological health screen values are presented in Appendix I.

No positive results were found during the health screens.

4.3. Postmortem Study Evaluations

The Pathology Report is presented in Appendix K.

4.3.1. Macroscopic

Interim

A test article-related macroscopic observation, “irregular surface” of the kidneys, was noted in the kidneys of one 500 mg/kg/day (high dose) female (animal number 1561). This observation

correlated with mild chronic progressive nephropathy in this animal and was indicative of a slight increase in severity of chronic progressive nephropathy in the 500 mg/kg/day female group at one year. Other macroscopic observations were considered incidental and typical of lesions seen in rats of this strain and age.

Terminal

No test article-related macroscopic observations were noted in males. In females, test article-related macroscopic observations were noted in the kidneys and liver. In the kidneys, "irregular surface" was noted in 16 of 70 animals at 500 mg/kg/day (not present in controls or any of the lower dose groups), while in the liver, "tan focus/foci" was noted in 1, 1, 1, 8 of 70 animals each at 0, 1, 50, and 500 mg/kg/day, respectively, and "mass/nodule" was noted in 14 of 70 animals at 500 mg/kg/day (not present in controls or any of the lower dose groups). These macroscopic observations were correlative to test article-related microscopic findings described below.

4.3.2. Organ Weights

Interim

Test article-related organ weight changes were limited to the high dose groups. Increased liver weights occurred in males at 50 mg/kg/day and in female rats at 500 mg/kg/day. In males, the increase was small and only the mean liver relative to body weight was statistically significantly increased (14.53% above control). In females, the liver weight increase was larger (mean liver relative to body weight was 66.75% above control) and all parameters (absolute and relative to both brain and body weight) were statistically significantly increased. The liver weight changes in the affected male and female groups were associated with microscopic changes in the liver (discussed below).

Mean final body weight at the interim necropsy was 19.51% less than control in the 500 mg/kg/day females. As a result of this decrement in mean final body weight, the brain, kidney, and thyroid/parathyroid relative to body weight were statistically significantly increased. Aside from a slight increase in severity of chronic progressive nephropathy in the kidneys, there were no microscopic changes in these organs associated with the increased weights, and mean absolute weights were not increased. Thus, these changes were considered secondary to the body weight decrement at 500 mg/kg/day. Additionally, mean absolute and relative to brain weights of the spleen in the 500 mg/kg/day females were statistically significantly lower than controls. These differences were not considered test article-related, as there were no microscopic changes in the spleen in either sex.

Terminal

No test article-related or statistically significant organ weight changes occurred in males.

In females, the only test article-related effect on organ weights was an increase in liver weights at 500 mg/kg/day. Mean absolute and relative to both body and brain weights were increased compared to control, with mean liver relative to body weight 41.61% greater than control. There

were several test article-related microscopic changes to account for the increased weights, as described below.

4.3.3. Microscopic

Interim

Test article-related microscopic findings were noted in the liver of both male and female rats, and in the kidneys of females, in the high-dose groups (50 and 500 mg/kg/day for males and females, respectively).

In males, there was a slight increase in minimal focal cystic degeneration of the liver (0, 0, 0, 3 at 0, 0.1, 1, and 50 mg/kg/day, respectively). This finding was more pronounced in the terminal portion of the study. Also in males, there was a slight increase in minimal to mild focal necrosis of the liver (1, 1, 0, 5 at 0, 0.1, 1, and 50 mg/kg/day, respectively).

In females, the only microscopic finding in the liver was centrilobular hypertrophy, which occurred in all 10 of the 500 mg/kg/day females. This change was of minimal severity and was characterized primarily by a slight increase in size of centrilobular hepatocytes with increased red granularity to the cytoplasm and is consistent with peroxisome proliferation. Also in females, there was a very slight increase in incidence and severity of chronic progressive nephropathy in the kidneys at 500 mg/kg/day. This change was characterized by foci of basophilic tubules, some with thickening of basement membranes. In the 500 mg/kg/day group, most incidences were of mild severity, while in the other groups, including controls, the incidences were primarily of minimal severity, although in a single control female the incidence was of moderate severity.

Incidences And Severity of Chronic Progressive Nephropathy in the Kidneys of Female Rats: Interim Sacrifice

Dose level: mg/kg/day		**0**	**1**	**50**	**500**
Kidney					
Nephropathy, chronic progressive		6	4	6	9
	-minimal	5	3	4	3
	-mild	0	1	2	6
	-moderate	1	0	0	0

In males, there was a single interstitial cell adenoma of the testes at 50 mg/kg/day; incidences of interstitial cell hyperplasia were 1, 0, 0, 3 at 0, 0.1, 1, and 50 mg/kg/day. The incidences of these changes in treated groups were not statistically different from controls (historical data for rats of this age were not available). Proliferative interstitial cell lesions are discussed in more detail under microscopic findings for the terminal sacrifice. All other microscopic findings were considered incidental, and typical of those seen in rats of this strain and age.

Terminal

Non-neoplastic

Test article-related non-neoplastic microscopic changes were observed in the liver of males and in the liver, kidneys, nonglandular stomach (limiting ridge), and tongue of females at the highest doses tested, 50 mg/kg/day in males and 500 mg/kg/day in females.

Liver

In the liver of males at 50 mg/kg/day there were statistically significantly increased incidences of focal cystic degeneration, centrilobular hepatocellular hypertrophy, and centrilobular hepatocellular necrosis. Cystic degeneration was characterized by the presence of multilocular cystic spaces containing finely granular or flocculent material without endothelial or epithelial cells lining the spaces. Centrilobular hypertrophy, morphologically consistent with peroxisome proliferation, was characterized by hepatocytes with red granular cytoplasm sometimes containing small amounts of pigment morphologically compatible with lipofuscin. Centrilobular hepatocellular necrosis was typically of the coagulative type with strongly eosinophilic-staining cytoplasm and pyknotic nuclei.

Test article-related findings in the liver of females at 500 mg/kg/day were similar to those noted in males at 50 mg/kg/day, and also included low incidences of panlobular hepatocellular hypertrophy and individual cell hepatocellular necrosis. Panlobular hepatocellular hypertrophy was characterized by enlargement of hepatocytes (as described above for centrilobular hypertrophy) throughout the entire liver. Individual cell necrosis was characterized by the presence of scattered single hepatocytes with features characteristic of apoptosis.

Summary of Selected Non-neoplastic Findings in the Liver of Male and Female Rats				
Dose level: mg/kg/day	**0**	**0.1**	**1**	**50**
Male				
Degeneration, cystic, focal	24/70 (34.29%)	24/70 (34.29%)	19/70 (27.14%)	42/70#* (60.00%)
Hypertrophy, hepatocyte, centrilobular	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	7/70#* (10.00%)
Necrosis, hepatocytes, centrilobular	1/70 (1.43%)	0/70 (0.00%)	1/70 (1.43%)	5/70# (7.14%)
Dose level: mg/kg/day	**0**	**1**	**50**	**500**
Female				
Degeneration, cystic, focal	2/70 (2.86%)	2/70 (2.86%)	2/70 (2.86%)	14/70#* (20.00%)
Hypertrophy, hepatocyte, centrilobular	0/70 (0.00%)	0/70 (0.00%)	3/70 (4.29%)	65/70#* (92.86%)
Hypertrophy, hepatocyte, panlobular	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	3/70# (4.29%)
Necrosis, hepatocytes, centrilobular	1/70 (1.43%)	1/70 (1.43%)	4/70 (5.71%)	7/70# (10.00%)
Necrosis, individual hepatocyte	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	3/70# (4.29%)
# - Statistically significant by Cochran-Armitage trend test ($p<0.05$)				
* - Statistically significant by Fisher's exact test ($p< 0.05$)				

Kidneys

Statistically significantly increased microscopic findings in the kidneys of females at 500 mg/kg/day included tubular dilatation, edema of the renal papilla, transitional cell hyperplasia in the renal pelvis, tubular mineralization, renal papillary necrosis, and chronic progressive nephropathy. Tubular dilatation frequently occurred in an ascending pattern extending from the papilla to the outer cortex, while at other times it was more prominent in the papilla. Edema of the papilla was characterized by increased rarefaction or myxomatous change in the papillary interstitium, sometimes with polypoid protrusions from the lateral surface of the papilla. The edema and tubular dilatation were often associated with hyperplasia of the transitional cell epithelium lining the papilla and pelvis. In some animals, necrosis of the tip of the papilla was present. In some 500 mg/kg/day females with the renal papillary changes, lesions diagnosed as chronic progressive nephropathy (CPN) were comprised of dilated tubules (often in an ascending pattern as described above), mononuclear cell infiltrates, and basophilic tubules, but with less thickening of tubular basement membranes than typically seen in CPN. In

these animals, the constellation of lesions diagnosed as CPN may be more representative of retrograde nephropathy as described by Hard, et al.[14], rather than typical CPN.

Summary of Selected Non-neoplastic Findings in the Kidneys of Female Rats				
Dose level: mg/kg/day	**0**	**1**	**50**	**500**
Dilatation, tubular	4/70 (5.71%)	2/70 (2.86%)	5/70 (7.14%)	28/70#* (40.00%)
Edema, papilla	4/70 (5.71%)	1/70 (1.43%)	2/70 (2.86%)	43/70#* (61.43%)
Hyperplasia, transitional cell	6/70 (8.57%)	3/70 (4.29%)	12/70 (17.14%)	33/70#* (47.14%)
Mineralization, tubular	25/70 (35.71%)	32/70 (45.71%)	28/70 (40.00%)	42/70#* (60.00%)
Necrosis, papillary	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	16/70#* (22.86%)
Nephropathy, chronic progressive	39/70 (55.71%)	40/70 (57.14%)	41/70 (58.57%)	64/70#* (91.43)

- Statistically significant by Cochran-Armitage trend test ($p<0.05$)
* - Statistically significant by Fisher's exact test ($p< 0.05$)

The nonglandular stomach (limiting ridge only) and the tongue had statistically significantly increased incidences of hyperplasia of squamous epithelium at 500 mg/kg/day. In the tongue, subacute/chronic inflammation occurred in association with squamous epithelial cell hyperplasia. There is no data describing incidence of epithelial hyperplasia of the limiting ridge of the nonglandular stomach in the historical control database for 2 year studies. The incidence of squamous cell hyperplasia of the tongue at 500 mg/kg/day (18.6%) exceeds the historical control range of 0-3.3%.[15] There was also a single incidence of squamous cell carcinoma (1.4%) in the tongue of females at 500 mg/kg/day. This is well within the historical control range of 0-1.7%[16] and the finding of a single such tumor was not considered a direct result of test article administration.

Summary of Selected Non-neoplastic Findings in the Nonglandular Stomach and Tongue of Female Rats				
Dose level: mg/kg/day	**0**	**1**	**50**	**500**
Stomach, nonglandular				
Hyperplasia, epithelial, limiting ridge	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	9/70#* (12.86%)
Tongue				
Hyperplasia, squamous cell	2/70 (2.86%)	8/70 (11.43%)	4/70 (5.71%)	13/70#* (18.57%)
Inflammation, subacute/chronic	3/70 (4.29%)	8/70 (11.43%)	4/70 (5.71%)	13/70#* (18.57%)
# - Statistically significant by Cochran-Armitage trend test ($p<0.05$) * - Statistically significant by Fisher's exact test ($P < 0.05$)				

Other

A statistically significant increase in the incidence of alveolar histiocytosis was present in females at 500 mg/kg/day. The incidences were 22, 20, 21, 42 (61%) at 0, 1, 50, and 500 mg/kg/day, respectively. The incidence at 500 mg/kg/day was statistically significant by both the Fisher Exact test and the Cochran-Armitage trend test and is at the upper end of the historical control range of 9.2-61.7%.[15] The increased incidence of this common background finding may be secondary to aspiration of dosing formulation at this high concentration; however, a definitive mechanism for this increase could not be determined.

A slight but statistically higher (by the Cochran-Armitage Trend test) incidence of pancreatic acinar cell hyperplasia occurred in females at 50 and 500 mg/kg/day; incidences were 0, 2, 5, 5 (7.1%) at 0, 1, 50, and 500 mg/kg/day, respectively. The incidences of acinar cell hyperplasia at the two highest doses slightly exceeded the historical control range of 0-4.6%,[15] but were not significant by the Fisher Exact test and were not associated with pancreatic acinar cell tumors. In addition, acinar cell hyperplasia did not occur in a clear dose response manner, as incidences in the 50 and 500 mg/kg/day groups were the same despite the order of magnitude difference in dose. In contrast, all other test article-related changes observed at 500 mg/kg/day occurred with a clear dose response. Therefore, the slight increase in acinar cell hyperplasia in the 50 and 500 mg/kg/day females was considered most likely spurious and not test article-related.

A statistically significant increase (by both the Fisher Exact test and the Cochran-Armitage trend test) in the incidence of alopecia/hypotrichosis was present in females at 500 mg/kg/day. The incidences were 1/70, 2/48, 5/55, and 9/70 (12.9%). However, the relevance of alopecia/hypotrichosis is more appropriately made by interpretation of the incidence of this finding in the clinical observations of the study rather than the microscopic observations. Therefore, for microscopic purposes, this was not considered at potential target organ.

Finally, incidences of cataract of the lens of the eye, pelvic mineralization of the kidney, and angiectasis of the liver were statistically significantly increased. Cataract of the eye and angiectasis of the liver were statistically significantly increased by the Cochran-Armitage trend test at 500 mg/kg/day while pelvic mineralization of the kidney was statistically significantly increased by the Cochran-Armitage trend test and Fisher's exact test at 500 mg/kg/day, and Fisher's exact test at 1 mg/kg/day. Incidences of cataract of the eye were 0/69, 0/48, 0/55, and 3/70 (4.29%) at 0, 1, 50, and 500 mg/kg/day, respectively. The historical control range for cataract is 0 to 10.8%.[15] Incidences of pelvic mineralization of the kidney were 52/70, 63/70, 58/70, and 63/70 (90.0%) at 0, 1, 50, and 500 mg/kg/day, respectively. The historical control range is 45.0 to 87.7% (note: two studies in the historical control database with an incidence of 0/60 reflect that this change was simply not tracked as pelvic mineralization in the studies).[15] Incidences of angiectasis of the liver were 1/70, 0/70, 3/70, and 5/70 (7.14%) at 0, 1, 50, and 500 mg/kg/day, respectively. The historical control range is 0 to 10.0%.[15] For each of the changes, the incidence was well within the historical control range, except pelvic mineralization, which is a very common background finding, only slightly exceeded the historical control range. Thus, these changes were not considered test article-related.

All other non-neoplastic microscopic observations were of the type typically seen in rats of this strain and age, and were considered incidental and not related to test article administration.

Neoplastic

Test article-related neoplastic changes occurred in the liver of females administered 500 mg/kg/day, the highest dose tested in females. Equivocal increases in pancreatic acinar cell tumors and testicular interstitial (Leydig) cell tumors occurred in males administered 50 mg/kg/day, the highest dose tested in males.

Liver

In females, hepatocellular adenoma occurred with an incidence of 0, 0, 0, and 11 (15.71%) at 0, 1, 50, and 500 mg/kg/day, respectively (statistically significant by the pairwise Fisher Exact test, the Cochran-Armitage trend test and the Peto test). Hepatocellular carcinoma occurred with an incidence of 0, 0, 0, 4 (5.71%) at 0, 1, 50, and 500 mg/kg/day, respectively (statistically significant by the Cochran-Armitage trend test and the Peto test, but not the Fisher Exact test). The incidences of both adenoma and carcinoma exceeded the historical control range (hepatocellular adenoma: 0-5.0%; hepatocellular carcinoma: 0-1.7%).[16] The increased incidences of hepatocellular tumors in the 500 mg/kg/day female group occurred in association with degenerative/necrotic changes in the liver at this dose level (see above under discussion of non-neoplastic lesions).

No hepatocellular tumors were observed in females administered 1 or 50 mg/kg/day, and no test article-related degenerative or necrotic changes occurred in the livers at these concentrations. Few hepatocellular tumors occurred in males and the incidence was essentially no different between the controls and the 50 mg/kg/day group, the highest dose tested. Hepatocellular adenomas occurred with an incidence of 1, 2, 1, 1 at 0, 0.1, 1, and 50 mg/kg/day, respectively,

while hepatocellular carcinoma occurred with an incidence of 1, 0, 0, 2 at 0, 0.1, 1, and 50 mg/kg/day, respectively.

Pancreas

In males, the only statistically significant increase in any tumor type occurred in the pancreas. In high-dose males administered 50 mg/kg/day, the incidences of pancreatic acinar cell adenoma/carcinoma combined—but not adenoma or carcinoma alone—were statistically significantly increased. Incidences of pancreatic acinar cell adenoma were 0, 1, 0, 3 (4.29%) at 0, 0.1, 1, and 50 mg/kg/day, respectively. The increased incidence at 50 mg/kg/day was not statistically significant by either the Cochran-Armitage trend test, the Peto test, or the pairwise Fisher Exact test, and was within the laboratory historical control range of 0-5.0%.[16] Two carcinomas (2.86%) were also observed in the 50 mg/kg/day male group (not statistically significant but slightly outside the historical range of 0-1.7%),[16] so the incidences of adenoma/carcinoma combined were 0, 1, 0, 5, respectively. The combined incidence of adenoma and carcinoma (5/70) at 50 mg/kg/day was significant by both the Cochran-Armitage trend test and the Peto test but not by the Fisher Exact test.

Since pancreatic acinar cell hyperplasia and adenoma in rats occur along a continuum, the incidence of acinar cell hyperplasia is also expected to be increased when a test-article related increase in acinar cell adenoma is observed. However, the incidences of acinar cell hyperplasia were not significantly different from controls in any of the treated male groups (incidences of acinar cell hyperplasia were 16, 18, 7, 21 at 0, 0.1, 1, and 50 mg/kg/day, respectively).

In summary, the incidences of acinar cell adenoma/carcinoma combined in the 50 mg/kg/day male group were statistically increased and slightly outside historical controls, but were not associated with statistically significant increases in either acinar cell adenoma or carcinoma alone nor with increases in acinar cell hyperplasia. Based on these considerations, and the known PPARα agonist activity of the test article, the marginal increase in pancreatic acinar cell tumors in the 50 mg/kg/day male group provides equivocal evidence of a test article-related effect.

Testes

The incidences of interstitial cell adenoma of the testes were 4, 4, 1, 8 (11.43%) at 0, 0.1, 1, and 50 mg/kg/day in the male groups, respectively (as noted above, an interstitial cell adenoma was also present in one male in the 50 mg/kg/day group at the interim sacrifice). These incidences were not statistically significant by the pairwise Fisher Exact test, the Cochran-Armitage trend test or the Peto test, but slightly exceeded the historical control range of 0-8.3%.[16] The incidences of interstitial cell hyperplasia were 7, 7, 3, 15 (21.4%) at 0, 0.1, 1, and 50 mg/kg/day, respectively. These incidences of hyperplasia were also not statistically significant by pairwise or trend analysis. The laboratory historical range for interstitial cell hyperplasia is 0-8.3% (the same as that for adenoma).[15] Thus, in the current study, the incidences of interstitial cell hyperplasia in both treated and control groups (with the exception of the 1 mg/kg/day group) exceeded the historical range.

Since PPARα agonists are known to produce proliferative interstitial cell lesions (hyperplasia and adenoma) in the testes of rats, a relationship to treatment for these findings in the 50 mg/kg/day male group cannot be ruled out. However, based on the marginal nature of the increased incidences of these lesions, their lack of statistical significance, and the relatively high incidence of these lesions in concurrent controls, the relationship to treatment for these findings is equivocal. There were no test article-related increases in proliferative interstitial cell lesions of the testes in the 0.1 and 1 mg/kg/day groups, as the incidences of interstitial cell tumors and hyperplasia were similar to or less than controls in the 0.1 and 1 mg/kg/day groups.

Other

All other statistically significant increases in neoplastic lesions occurred in females and were considered to represent the spontaneous occurrence of neoplasms commonly seen in rats of this strain and age.

Uterine stromal polyps occurred with an incidence of 1, 2, 1, 7 (10.0%) for 0, 1, 50, and 500 mg/kg/day, respectively. The increased incidence at 500 mg/kg/day was statistically significant by the Cochran-Armitage trend test and the Peto test, but was not statistically significant by the Fisher Exact test and was well within the historical control range of 0-13.8%.[16] Therefore, this finding was not considered to be test article-related.

Finally, adenoma of the pars distalis of the pituitary gland was statistically increased by the pairwise Fisher Exact test at 1 and 50 mg/kg/day. These increases did not occur in a dose-related manner, as the incidence of pituitary adenoma in 500 mg/kg/day females was not statistically different from controls. In addition, the incidence of this tumor in all groups was within the laboratory historical range of 59.2-91.1%.[16] Pars distalis adenomas occurred with an incidence of 53/70 (75.71%), 58/65 (89.23%), 58/65 (89.23%), 52/70 (74.29%) at 0, 1, 50, and 500 mg/kg/day, respectively. Thus, since the incidences at 1 and 50 mg/kg/day are within the historical control range and are also not dose-related, they were not considered test article-related. Further, when the incidence of pituitary gland adenoma and carcinoma are combined there is no statistical significance at any dose.

No other tumor types were statistically significantly increased in either sex.

The test article belongs to a class of compounds known as peroxisome proliferators (PPARα agonists)[17], which are known to produce liver, pancreatic, and testicular tumors in rats, and liver tumors in mice.[18, 19] However, these compounds have not been shown to be carcinogenic in other species, including humans.[19, 20] Based on extensive research into the comparative biology of peroxisome proliferator-induced hepatic carcinogenesis, the induction of liver tumors in rodents by non-genotoxic peroxisome proliferators is not considered relevant to humans.[20, 21, 22] Furthermore, while less definitive mechanistic data are available on the role PPARα in the induction of pancreatic acinar cell tumors in rats, the available data on a proposed mode of action involving altered bile flow and increased cholecystokinin (CCK) suggest that this mode of action is also likely not relevant to humans.[22] Mechanistic data on the mode of action for induction of testicular interstitial cell tumors in rats by peroxisome proliferators is less robust.[22] However, extensive research into the comparative biology and mechanisms of action of interstitial cell

tumor induction in rodents by a wide class of non-genotoxic compounds indicate that these tumors most likely have low relevance to humans under most exposure condition.[23, 24]

4.3.4. Pathology Conclusions

Following oral (gavage) exposure of male and female rats to the test article for up to two-years, test article-related changes in pathology parameters were limited to the high dose groups (50 and 500 mg/kg/day in males and females, respectively). Non-neoplastic changes occurred in the kidneys, liver, squamous regions of the gastrointestinal tract, and lung of 500 mg/kg/day females, and in the liver of 50 mg/kg/day males. Neoplastic (and/or hyperplastic) changes included hepatocellular tumors in 500 mg/kg/day females and, equivocally, pancreatic acinar cell tumors and testicular interstitial cell tumors in 50 mg/kg/day males. All tumors occurred with a clear dose-related threshold, as no hepatocellular tumors were observed in females at lower doses, the only pancreatic acinar cell tumor that occurred below 50 mg/kg/day was an adenoma that occurred at 0.1 mg/kg/day (not dose-related and well within the historical control range of 0-5.0%[14]), and the incidences of interstitial cell tumors and hyperplasia in males at lower doses were less than or equal to those of controls. In females, liver tumors occurred in association with marked systemic toxicity, as well as liver toxicity.

The induction of liver tumors in female rats at 500 mg/kg/day, and the equivocal increase in pancreatic acinar and testicular interstitial cell tumors in male rats at 50 mg/kg/day are likely not relevant to humans based on the following: most research indicates that induction of these specific tumors in rats by non-genotoxic peroxisome proliferators likely has little or no relevance to humans, especially in plausible human exposure scenarios; the test material was determined to be non-genotoxic based on a battery of *in vivo* and *in vitro* genotoxicity studies; liver tumors were produced only in females and only at doses associated with marked hepatic and systemic toxicity (including lethality); and thresholds were established for all tumor types.

No adverse pathology findings occurred in male rats administered 0.1 or 1 mg/kg/day or in females administered 1 or 50 mg/kg/day.

5. CONCLUSIONS

Under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for chronic toxicity of was 1 mg/kg/day in male rats and 50 mg/kg/day in females. The NOAEL in males is based on increases in focal cystic degeneration, focal necrosis, and centrilobular necrosis of the liver, with associated increases in cytotoxic liver enzymes, and equivocal increases in pancreatic acinar cell tumors and testicular interstitial (Leydig) cell tumors, all observed at 50 mg/kg/day. In females the NOAEL is based on reductions in body weight, body weight gain, and food efficiency; mild decreases in red cell mass; increases in individual cell necrosis in the liver, hyperplasia and/or inflammation in the nonglandular stomach and tongue; an increase in incidence and severity of microscopic pathology in the kidneys; and an increase in hepatocellular adenomas and carcinomas, all observed at 500 mg/kg/day.

Test article-related increases in hepatocellular adenoma and hepatocellular carcinoma were observed in females at 500 mg/kg/day. Equivocal increases in pancreatic acinar cell tumors and testicular interstitial (Leydig) cell tumors occurred in males administered 50 mg/kg/day. Clear thresholds were established for all of these tumor types, as test article-related tumor responses occurred only at the highest doses tested in males and females. Most research indicates that induction of these specific tumors in rats by non-genotoxic peroxisome proliferators likely has little or no relevance in humans, especially in plausible human exposure scenarios.

6. REFERENCES

1. Principles for the utilization and care of vertebrate animals used in testing, research, and training. Federal Register, 1985 May 20; 50(97).

2. Position statement on the use of animals in research. 1993 Feb 26; NIH Guide 22(8).

3. Milliken GA, Johnson DE. Analysis of messy data. London: Chapman and Hall: 1992.

4. Dunnett, CW. A multiple comparison procedure for comparing several treatments with a control. J Am Stat Assoc 1955; 50:1096-1121.

5. Welch BL. The significance of difference between two means when the population variances are unequal. Biometrika 1937; 29:350-362.

6. Steel RGD, Torrie JH. Principles and procedures of statistics. A biometrical approach. New York: McGraw-Hill; 1980.

7. Allison PD. Survival analysis using the SAS system: A Practical Guide. Cary (NC). SAS Institute Inc.; 1995.

8. Agresti A. Categorical data analysis. 2nd ed. New York: John Wiley and Sons; 2002.

9. Zar JH. Biostatistical Analysis. 4th ed. New Jersey: Prentice Hall; 1999.

10. Peto R, Pike MC, Day NE, Gray RG, Lee PN, Parish S, Pete J, Richards S, Wahrendorf J. Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. In: Long-term and short-term screening assays for carcinogens: a critical appraisal. Annex to Supplement 2. p. 311-426. International Agency for Research on Cancer, Lyon; 1980.

11. Haseman JK. A reexamination of false-positive rates for carcinogenesis studies. Fund Appl Toxicol 1983; 3:334-339.

12. A 28-Day Oral (Gavage) Toxicity Study of in Rats with a 28-DayRecovery
2008.

13. Gervois, P.; Kleemann, R.; Pilon, A.; Percevault, F.; Koenig, W.; Staels, B.; Kooistra, T.Global suppression of IL-6-induced acute phase response gene expression after chronic invivo treatment with the peroxisome proliferator activated receptor-alpha activatorfenofibrate. Journal of Biological Chemistry 2004, 279, 16154-16160.

14. Hard GC, Flake GP, Sills RC. Re-evaluation of Kidney Histopathology from 13-Week Toxicity and Two-Year Carcinogenicity Studies of Melamine in the

F344 Rat: Morphologic Evidence of Retrograde Nephropathy. Vet Pathol 46:1248 (2009); DOI: 10.1354/vp.08-VP-0317-F-FL.

15. Non-Neoplastic Historical Control Data, Male and Female Sprague Dawley Rat – Charles River Laboratories, 2 Year Studies, Version 4.0, June 2002 to October 2010.

16. Neoplastic Historical Control Data, Male and Female Sprague Dawley Rat – Charles River Laboratories, 2 Year Studies, Version 4.0, August 2001 to August 2011.

17. . A 28-Day Oral (Gavage) Toxicity Study of in Rats with a 28-Day Recovery. , 2008,

18. Biegel LB, Hurtt ME, Frame SR, Applegate M, Conner JC, and Cook JC. Comparison of the effects of Wyeth-14,643 in Crl:CD BR and Fisher rats. Fundam. Appl. Toxicol., 1992, 19:590-597.

19. Klaunig JE, Babich M., Baetcke KP, Cook JC, Corton JC, David RM, DeLuca JG, Lai DY, McKee RH, Peters JM, Roberts RA and and Fenner-Crisp, PA. PPARα Agonist-Induced Rodent Tumors: Modes of Action and Human Relevance. Critical Reviews in Toxicology, 2003, 33 (6) , pp. 655-780.

20. Cunningham ML, Collins BJ, Hejtmancik MR, Herbert RA, Travlos GS, Vallant MK, and Stout MD. Effects of the PPARα Agonist and Widely Used Antihyperlipidemic Drug Gemfibrozil on Hepatic Toxicity and Lipid Metabolism. 2010, PPAR Research , art. no. 681963.

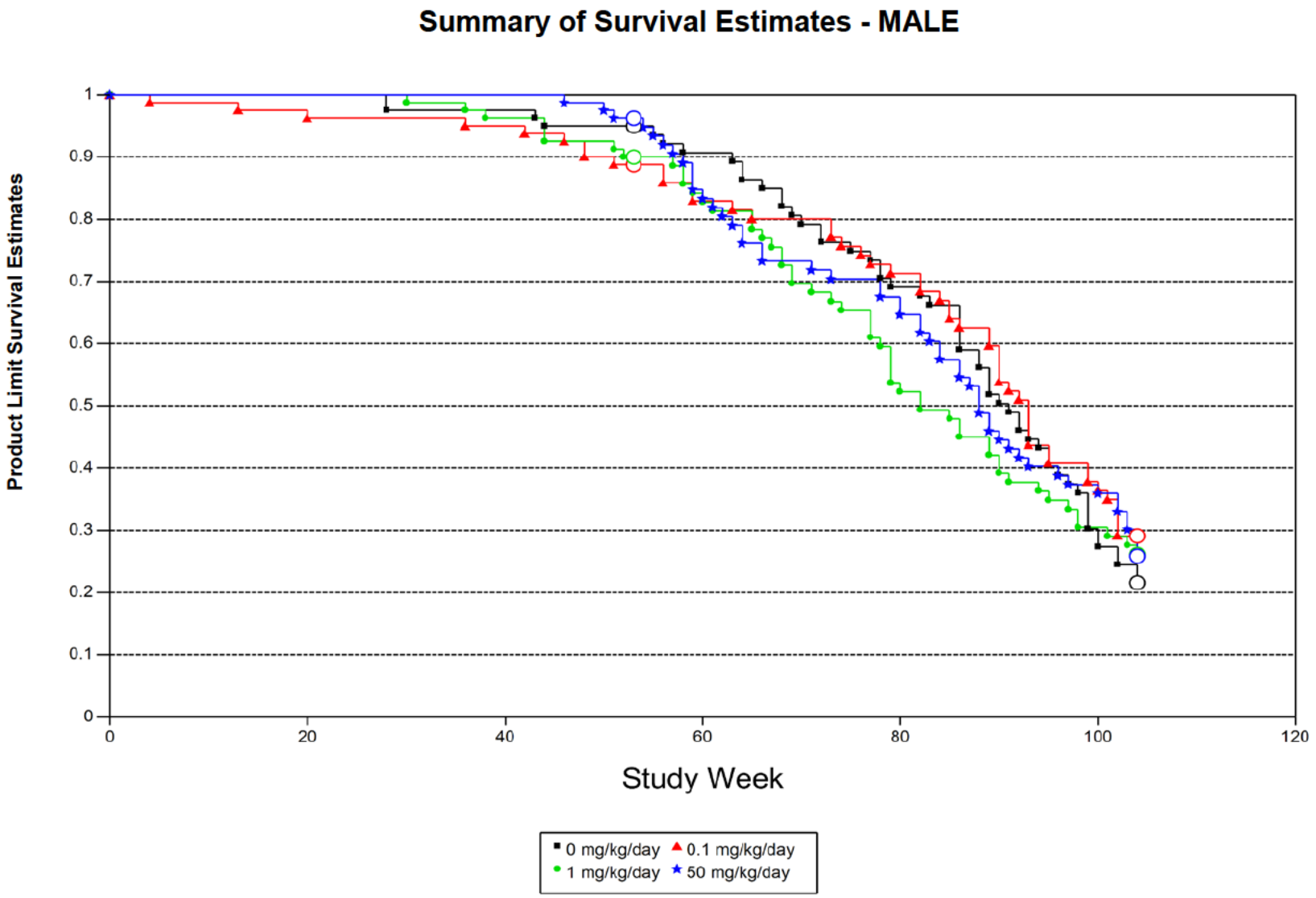
21. Peters JM, Cheung C and Gonzalez FJ. Peroxisome proliferator-activated receptor-α and liver cancer: where do we stand? J Mol Med (2005) 83: 774-785.

22. Klaunig JE, Hocevar BA, and Kamendulis LM. Mode of Action analysis of perfluorooctanoic acid (PFOA) tumorigenicity and Human Relevance. Reproductive Toxicology. Volume 33, Issue 4, July 2012, Pages 410-418.

23. Prentice DE and AW Meikle AW. A review of drug-induced Leydig cell hyperplasia and neoplasia in the rat and some comparisons with man. Human and Experimental Toxicology, 1995, 14:562-572.

24. Cook JC., Klinefelter GR, Hardisty .F, Sharpe RM and Foster PMD. Rodent Leydig cell tumorigenesis: A review of the physiology, pathology, mechanisms, and relevance to humans. Critical Reviews in Toxicology, 1999, 29(2): 169-261.

Figure 1
Summary of Survival Estimates


Summary of Survival Estimates - MALE
Product Limit Survival Estimates
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120
Study Week
0 mg/kg/day
0.1 mg/kg/day
1 mg/kg/day
50 mg/kg/day

Summary of Survival Estimates - FEMALE

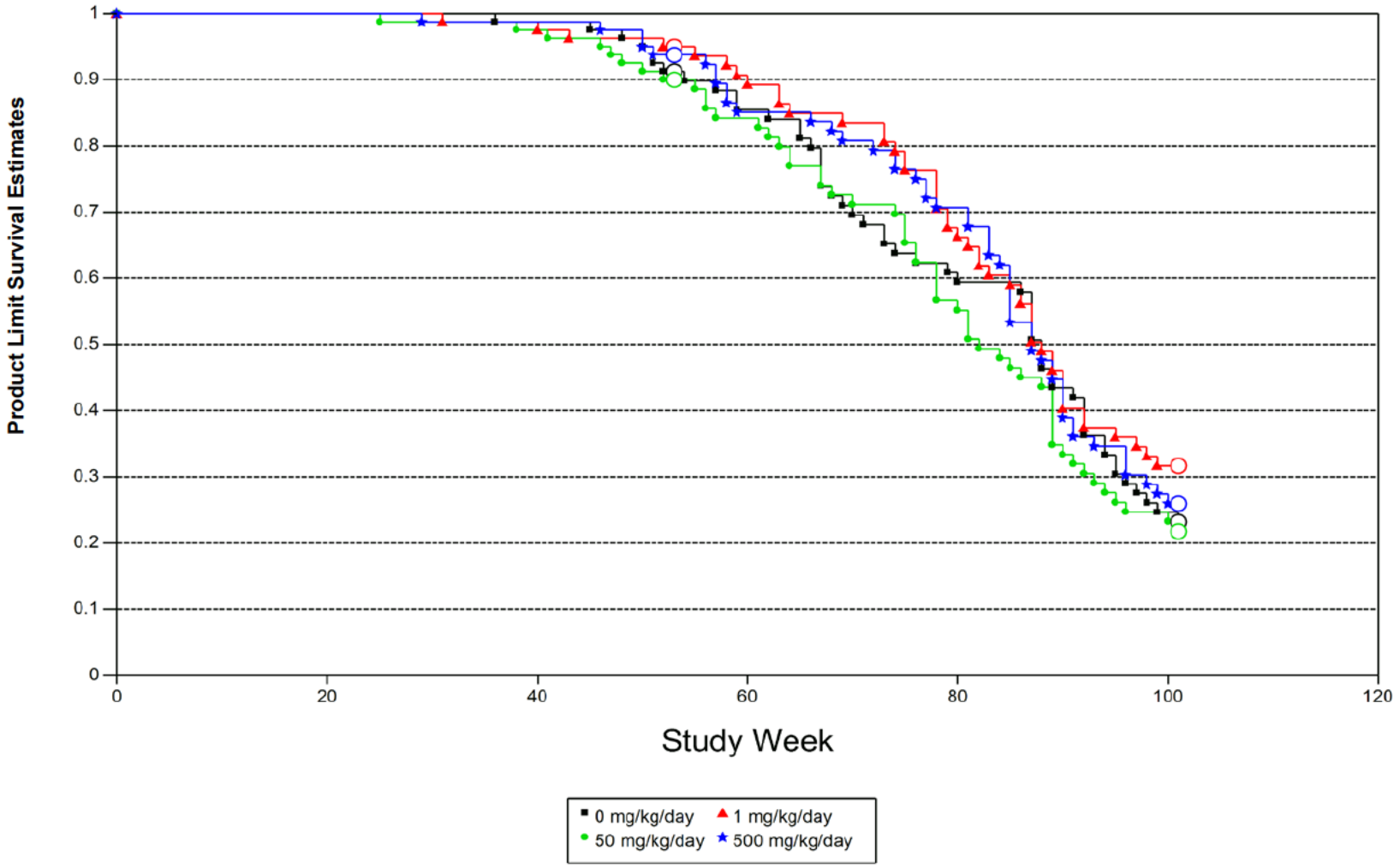


Figure 2
Mean Body Weight Values


Mean Body Weight Values - MALE
Weight, g
1000
900
800
700
600
500
400
300
200
0
20
40
60
80
100
Study Week
0 mg/kg/day
0.1 mg/kg/day
1 mg/kg/day
50 mg/kg/day

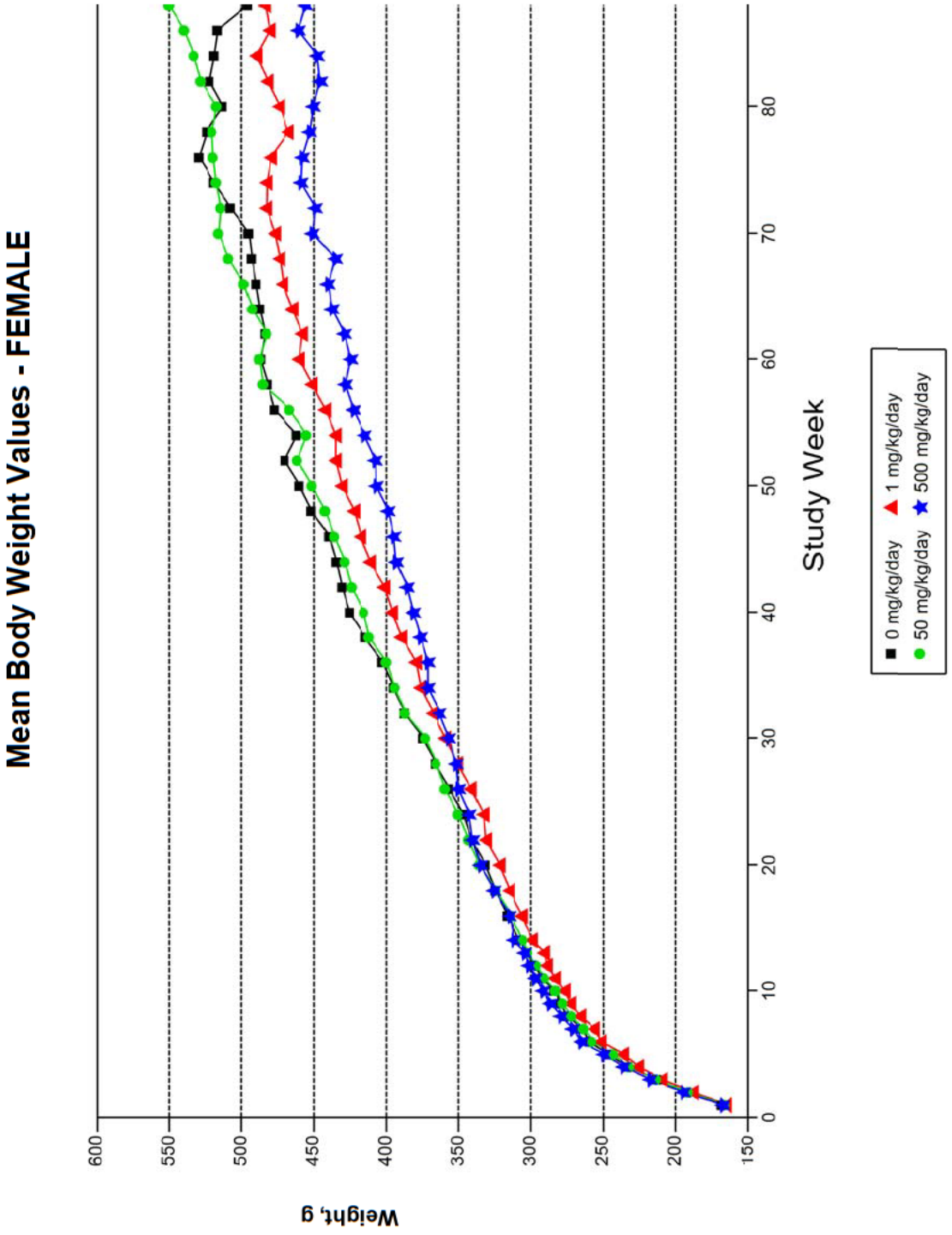
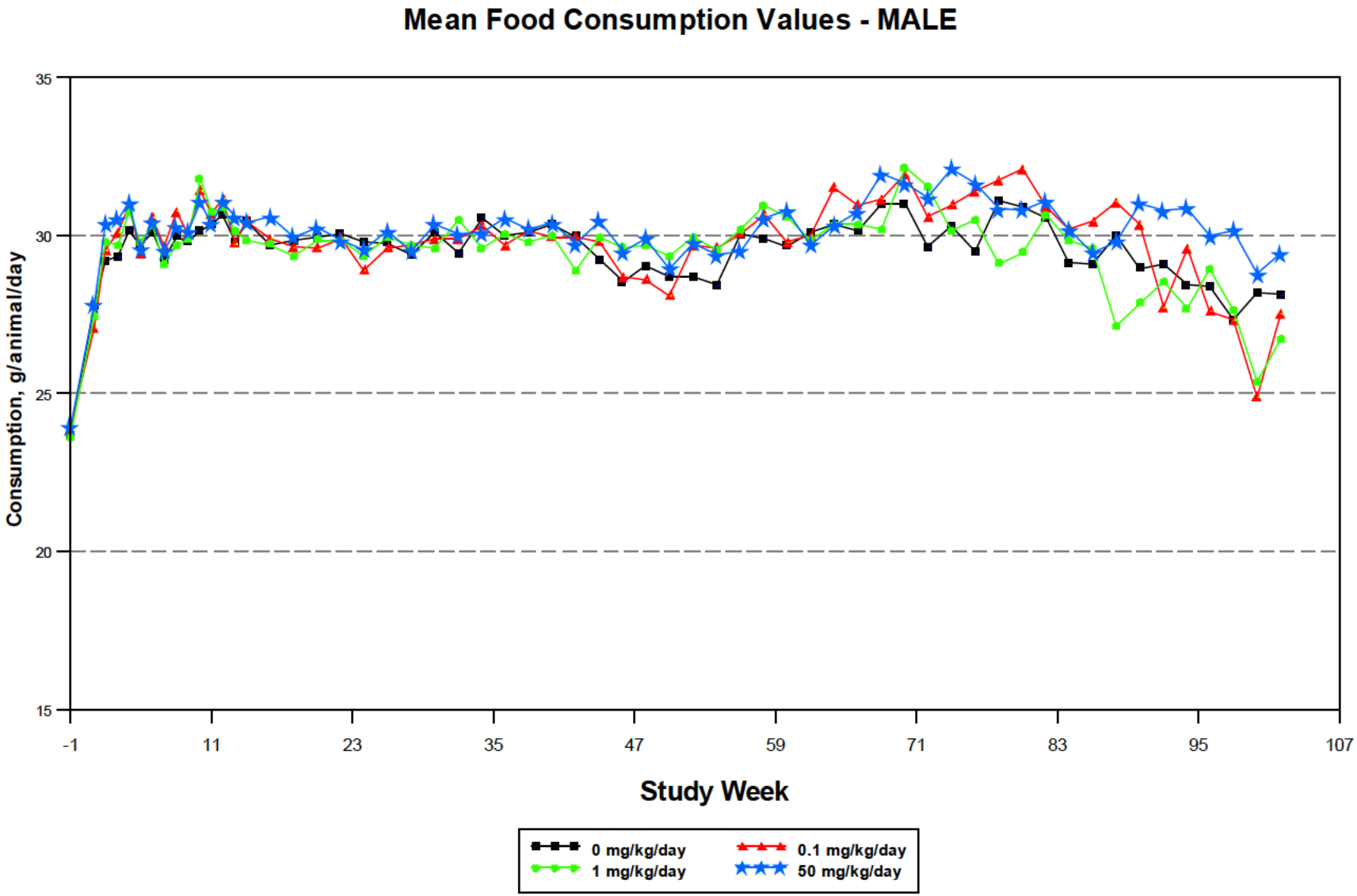

Mean Body Weight Values - FEMALE
Weight, g
600
550
500
450
400
350
300
250
200
150
0
10
20
30
40
50
60
70
80
Study Week
0 mg/kg/day
1 mg/kg/day
50 mg/kg/day
500 mg/kg/day

Figure 3
Mean Food Consumption Values


Mean Food Consumption Values - MALE
Consumption, g/animal/day
35
30
25
20
15
-1
11
23
35
47
59
71
83
95
107
Study Week
0 mg/kg/day
1 mg/kg/day
0.1 mg/kg/day
50 mg/kg/day

Mean Food Consumption Values - FEMALE

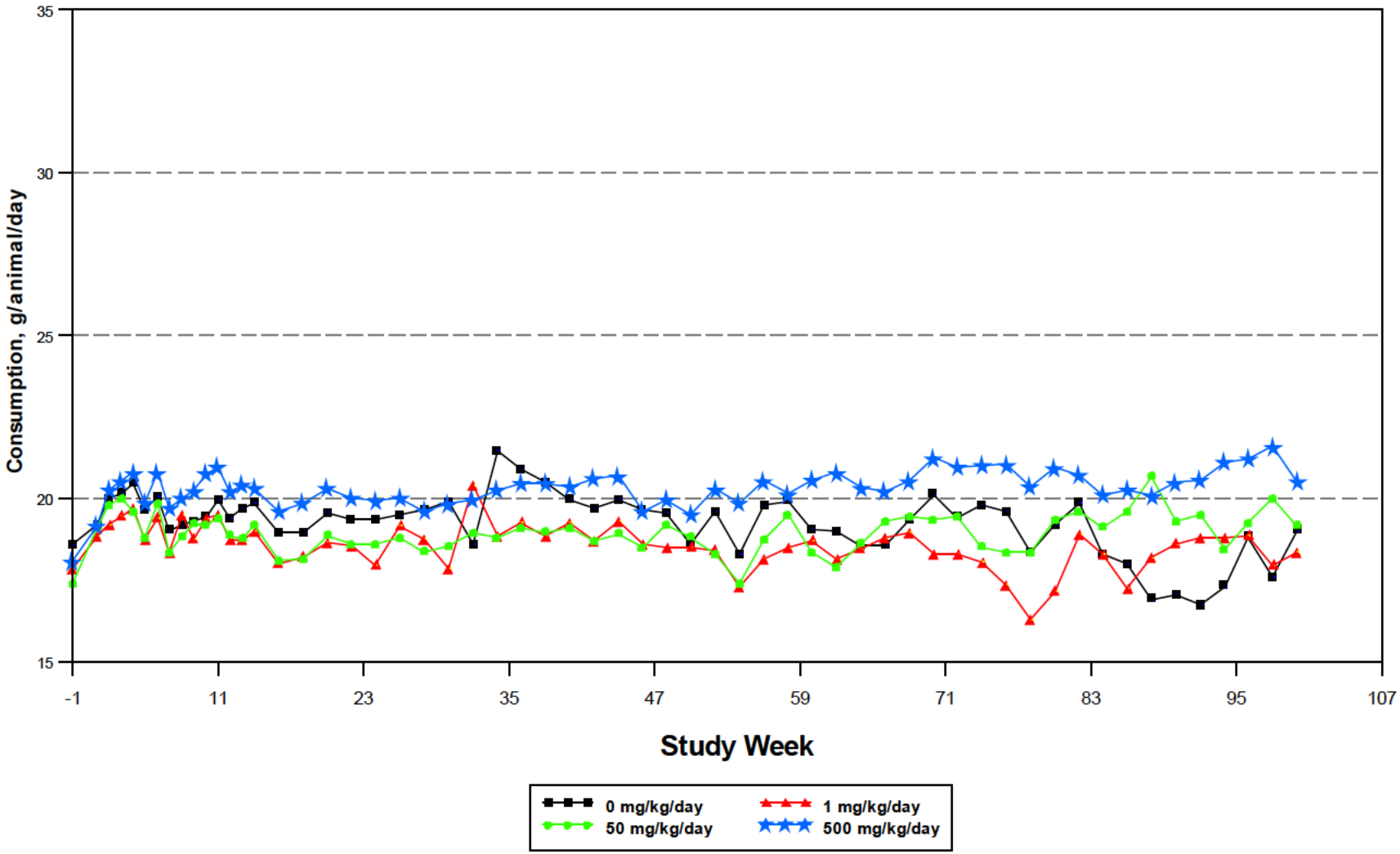


Table 1
Summary of Survival Estimates

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Survival Estimates - MALE*

Dose Level	Study Interval (Week)	Deaths	Censored	Effective Sample Size	Cumulative Survival	Survival Standard Error
0 mg/kg/day						
	1-13	0	0	80.0	1.0000	0.0000
	14-26	0	0	80.0	1.0000	0.0000
	27-39	2	0	80.0	1.0000	0.0000
	40-52	2	0	78.0	0.9750	0.0175
	53-65	6	10&	71.0	0.9500	0.0244
	66-78	11	0	60.0	0.8697	0.0385
	79-91	15	0	49.0	0.7103	0.0536
	92-104	19	15&	26.5	0.4928	0.0598
	105	0	0	0	0	0
0.1 mg/kg/day						
	1-13	2	0	80.0	1.0000	0.0000
	14-26	1	0	78.0	0.9750	0.0175
	27-39	1	0	77.0	0.9625	0.0212
	40-52	5	0	76.0	0.9500	0.0244
	53-65	6	10&	66.0	0.8875	0.0353
	66-78	5	0	55.0	0.8068	0.0449
	79-91	14	0	50.0	0.7335	0.0514
	92-104	16	20&	26.0	0.5281	0.0595
	105	0	0	0	0	0
1 mg/kg/day						
	1-13	0	0	80.0	1.0000	0.0000
	14-26	0	0	80.0	1.0000	0.0000
	27-39	3	0	80.0	1.0000	0.0000
	40-52	5	0	77.0	0.9625	0.0212
	53-65	8	10&	67.0	0.9000	0.0335
	66-78	13	0	54.0	0.7925	0.0463
	79-91	15	0	41.0	0.6017	0.0580
	92-104	8	18&	17.0	0.3816	0.0583
	105	0	0	0	0	0
50 mg/kg/day						
	1-13	0	0	80.0	1.0000	0.0000
	14-26	0	0	80.0	1.0000	0.0000
	27-39	0	0	80.0	1.0000	0.0000

& Necropsy count

* No statistical significance observed

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Survival Estimates - MALE*

Dose Level	Study Interval (Week)	Deaths	Censored	Effective Sample Size	Cumulative Survival	Survival Standard Error
50 mg/kg/day						
	40-52	3	0	80.0	1.0000	0.0000
	53-65	14	10&	72.0	0.9625	0.0212
	66-78	6	0	53.0	0.7753	0.0480
	79-91	17	0	47.0	0.6876	0.0543
	92-104	12	18&	21.0	0.4389	0.0594
	105	0	0	0	0	0

& Necropsy count

* No statistical significance observed

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Survival Estimates - FEMALE*

Dose Level	Study Interval (Week)	Deaths	Censored	Effective Sample Size	Cumulative Survival	Survival Standard Error
0 mg/kg/day						
	1-13	0	0	80.0	1.0000	0.0000
	14-26	0	0	80.0	1.0000	0.0000
	27-39	1	0	80.0	1.0000	0.0000
	40-52	6	0	79.0	0.9875	0.0124
	53-65	7	10&	68.0	0.9125	0.0316
	66-78	13	0	56.0	0.8186	0.0440
	79-91	14	0	43.0	0.6285	0.0572
	92-104	13	16&	21.0	0.4239	0.0592
	105	0	0	0	0	0
1 mg/kg/day						
	1-13	0	0	80.0	1.0000	0.0000
	14-26	0	0	80.0	1.0000	0.0000
	27-39	1	0	80.0	1.0000	0.0000
	40-52	3	0	79.0	0.9875	0.0124
	53-65	7	10&	71.0	0.9500	0.0244
	66-78	10	0	59.0	0.8563	0.0402
	79-91	21	0	49.0	0.7112	0.0535
	92-104	6	22&	17.0	0.4064	0.0588
	105	0	0	0	0	0
50 mg/kg/day						
	1-13	0	0	80.0	1.0000	0.0000
	14-26	1	0	80.0	1.0000	0.0000
	27-39	1	0	79.0	0.9875	0.0124
	40-52	6	0	78.0	0.9750	0.0175
	53-65	9	10&	67.0	0.9000	0.0335
	66-78	14	0	53.0	0.7791	0.0474
	79-91	17	0	39.0	0.5733	0.0587
	92-104	7	15&	14.5	0.3234	0.0563
	105	0	0	0	0	0
500 mg/kg/day						
	1-13	0	0	80.0	1.0000	0.0000
	14-26	0	0	80.0	1.0000	0.0000
	27-39	1	0	80.0	1.0000	0.0000

& Necropsy count

* No statistical significance observed

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Survival Estimates - FEMALE*

Dose Level	Study Interval (Week)	Deaths	Censored	Effective Sample Size	Cumulative Survival	Survival Standard Error
500 mg/kg/day						
	40-52	4	0	79.0	0.9875	0.0124
	53-65	6	10&	70.0	0.9375	0.0271
	66-78	10	0	59.0	0.8571	0.0400
	79-91	24	0	49.0	0.7119	0.0534
	92-104	7	18&	16.0	0.3632	0.0577
	105	0	0	0	0	0

& Necropsy count

* No statistical significance observed

Table 2
Summary of Detailed Clinical Observations

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Detailed Clinical Observations[+] - MALE

Weeks 1 to 104

Observation	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Observed	80	80	80	80
Number With No Abnormalities Detected	10	18	16	20
Animal Husbandry				
Teeth broken	6/2	1/1	3/3	11/1
Teeth cut	33/4	18/3	41/3	1/1
Teeth missing	76/1	0/0	0/0	0/0
Behavior/Activity				
Activity decreased	19/16	7/6	13/10	13/11
Ataxia	2/2	1/1	2/2	0/0
Head tilt	6/3	0/0	0/0	0/0
Hypersensitive to touch	5/3	0/0	2/2	63/8
Inappetence	1/1	1/1	2/2	0/0
Prostration	1/1	0/0	2/2	2/2
Righting reflex impaired	3/3	2/2	4/4	4/4
Righting reflex lost	1/1	1/1	2/2	2/2
Salivation	1/1	2/2	10/4	2/2
Stereotypy	0/0	0/0	0/0	1/1
Teeth chattering	1/1	0/0	2/2	2/2
Tremors	0/0	0/0	1/1	0/0
Vocalization	38/8	21/8	45/6	98/10
Dosing Observations				
Struggling during dosing	1/1	1/1	2/2	0/0

+ Number of times observed/Total number of animals affected

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Detailed Clinical Observations[+] - MALE
Weeks 1 to 104

Observation	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Excretion				
Feces few/absent	1/1	2/1	3/3	3/2
Feces soft	7/4	1/1	6/1	0/0
Feces watery	3/2	0/0	3/2	0/0
Material in pan/bedding, Red	0/0	0/0	1/1	0/0
Urine discolored, Red	1/1	0/0	2/2	0/0
External Appearance				
Abdomen distended	0/0	0/0	0/0	2/1
Body rigid	0/0	0/0	0/0	13/3
Carriage high	1/1	0/0	0/0	0/0
Carriage low	21/11	3/3	6/5	13/4
Digit(s) missing	0/0	0/0	0/0	9/1
Discharge, Red	8/4	3/1	2/2	2/2
Discharge, Yellow	0/0	0/0	1/1	0/0
Ear/portion of ear missing	0/0	0/0	58/1	0/0
Fracture	0/0	0/0	0/0	1/1
Lacrimation	22/2	6/1	45/3	12/1
Limb function impaired	10/5	7/6	21/9	37/4
Limb function lost	2/1	0/0	0/0	0/0
Malocclusion	91/2	1/1	39/1	19/1
Material around eyes, Black	54/5	1/1	14/3	13/2
Material around eyes, Brown	0/0	4/1	0/0	0/0
Material around eyes, Red	41/4	10/4	18/5	22/7

+ Number of times observed/Total number of animals affected

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Detailed Clinical Observations[+] - MALE

Weeks 1 to 104

Observation	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
External Appearance				
Material around mouth, Red	2/1	1/1	8/1	1/1
Material around mouth, Tan	0/0	0/0	1/1	0/0
Material around nose, Black	2/1	2/1	2/2	0/0
Material around nose, Brown	24/4	8/2	10/1	0/0
Material around nose, Red	29/5	8/4	26/8	82/6
Penis extended	3/2	0/0	0/0	0/0
Posture hunched	30/10	14/7	13/4	19/6
Swelling	193/21	164/20	117/16	74/13
Tail bent	0/0	0/0	0/0	61/1
Thin	15/8	5/2	20/7	57/7
Eye/Ocular				
Eye discolored, Clear	0/0	0/0	0/0	56/2
Eye discolored, Cloudy	8/1	36/3	0/0	3/2
Eye discolored, Dark	0/0	1/1	0/0	0/0
Eye discolored, Pale	21/2	0/0	8/2	0/0
Eye discolored, White	8/1	14/1	48/1	22/1
Eye protruding	10/1	17/1	0/0	15/2
Eyelid partially/completely closed	4/2	10/3	7/4	5/3
General Status				
Moribund	2/2	2/2	0/0	2/2
Pelage/Skin				
Abrasion(s)	6/3	1/1	7/4	23/6

+ Number of times observed/Total number of animals affected

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Detailed Clinical Observations[+] - MALE
Weeks 1 to 104

Observation	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Pelage/Skin				
Hair absent	0/0	0/0	82/1	0/0
Hair discolored, Black	2/1	0/0	0/0	1/1
Hair discolored, Brown	131/11	66/8	30/6	4/3
Hair discolored, Red	0/0	0/0	5/3	48/3
Hair discolored, Tan	6/1	0/0	0/0	16/1
Hair discolored, Yellow	56/7	23/3	107/11	49/3
Hair sparse	1411/28	1339/24	2266/39	660/19
Hair wet	19/7	19/4	14/8	3/1
Laceration	0/0	0/0	0/0	1/1
Loss of skin elasticity	1/1	0/0	0/0	0/0
Nodule, 1-5 mm	109/10	255/16	192/17	207/11
Nodule, 5-20 mm	44/1	84/5	100/6	25/2
Nodule, >20 mm	0/0	5/1	1/1	0/0
Piloerection	41/12	7/5	32/7	10/5
Scabbed area	38/10	173/19	95/14	125/11
Skin cold to touch	0/0	0/0	4/4	2/2
Skin discolored, Brown	11/2	6/1	0/0	20/2
Skin discolored, Red	0/0	1/1	2/1	0/0
Skin warm to touch	13/1	0/0	0/0	0/0
Ulcer, >20 mm	0/0	1/1	0/0	0/0
Ulcer plantar/palmar, 1-5 mm	1/1	10/1	6/1	31/2
Ulcer plantar/palmar, 5-20 mm	10/1	0/0	0/0	0/0
Ulcer plantar/palmar, >20 mm	10/1	0/0	0/0	0/0

+ Number of times observed/Total number of animals affected

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Detailed Clinical Observations[+] - MALE
Weeks 1 to 104

Observation	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Pelage/Skin				
Unkempt appearance	68/15	72/13	45/15	55/9
Respiration				
Breathing audible	4/3	3/3	0/0	11/4
Breathing difficult	2/2	1/1	1/1	2/2
Breathing rapid	0/0	0/0	2/1	0/0
Breathing shallow	2/2	1/1	2/2	5/5
Breathing slow	4/1	0/0	0/0	1/1
Rales	1/1	0/0	0/0	0/0
Odor				
Odor	0/0	0/0	0/0	8/2

+ Number of times observed/Total number of animals affected

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Detailed Clinical Observations[+] - FEMALE
Weeks 1 to 101

Observation	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Observed	80	80	80	80
Number With No Abnormalities Detected	13	7	11	5
Animal Husbandry				
Teeth broken	3/1	9/1	0/0	2/1
Teeth cut	19/3	12/3	0/0	11/4
Behavior/Activity				
Activity decreased	38/17	13/10	11/10	7/6
Ataxia	0/0	1/1	1/1	1/1
Head tilt	9/8	11/5	12/7	3/3
Hypersensitive to touch	0/0	1/1	0/0	5/1
Inappetence	0/0	1/1	3/3	0/0
Leaning	0/0	5/2	0/0	0/0
Prostration	0/0	0/0	1/1	0/0
Righting reflex impaired	5/5	7/4	7/7	0/0
Righting reflex lost	1/1	1/1	1/1	0/0
Salivation	0/0	0/0	0/0	455/36
Stereotypy	0/0	0/0	7/1	0/0
Teeth chattering	0/0	0/0	1/1	0/0
Vocalization	0/0	9/2	0/0	0/0
Excretion				
Feces few/absent	2/1	0/0	1/1	1/1

+ Number of times observed/Total number of animals affected

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Detailed Clinical Observations[+] - FEMALE
Weeks 1 to 101

Observation	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Excretion				
Material in pan/bedding, Red	0/0	0/0	1/1	0/0
External Appearance				
Body rigid	0/0	0/0	0/0	3/1
Carriage high	1/1	1/1	3/2	0/0
Carriage low	4/2	2/2	0/0	1/1
Discharge, Clear	0/0	0/0	0/0	1/1
Discharge, Red	1/1	0/0	2/1	1/1
Ear/portion of ear missing	21/1	98/4	0/0	37/1
Lacrimation	0/0	6/1	0/0	3/2
Limb function impaired	26/3	0/0	1/1	0/0
Limb function lost	1/1	0/0	0/0	0/0
Malocclusion	3/1	107/3	0/0	0/0
Material around eyes, Black	9/3	22/7	2/2	26/3
Material around eyes, Brown	2/1	2/1	0/0	0/0
Material around eyes, Red	20/3	32/6	21/6	10/7
Material around mouth, Black	0/0	1/1	0/0	0/0
Material around mouth, Red	0/0	0/0	1/1	0/0
Material around nose, Black	20/6	4/2	16/3	0/0
Material around nose, Brown	0/0	0/0	8/4	0/0
Material around nose, Red	8/4	13/4	5/4	10/6
Posture hunched	50/17	30/12	11/8	20/10
Reproductive tract prolapsed	1/1	0/0	0/0	0/0

+ Number of times observed/Total number of animals affected

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Detailed Clinical Observations[+] - FEMALE
Weeks 1 to 101

Observation	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
External Appearance				
Swelling	509/40	498/38	417/36	305/35
Tail missing - portion	0/0	0/0	0/0	31/1
Thin	30/13	39/13	16/9	38/11
Eye/Ocular				
Eye discolored, Pale	0/0	0/0	4/1	4/2
Eye discolored, White	0/0	0/0	0/0	13/2
Eye protruding	0/0	0/0	1/1	38/3
Eyelid partially/completely closed	3/2	5/2	0/0	2/1
General Status				
Moribund	0/0	0/0	2/2	0/0
Pelage/Skin				
Abrasion(s)	4/1	19/3	22/3	15/1
Hair absent	0/0	4/2	22/1	0/0
Hair discolored, Brown	26/4	2/1	0/0	20/5
Hair discolored, Red	2/2	2/1	0/0	0/0
Hair discolored, Tan	21/2	0/0	0/0	198/6
Hair discolored, Yellow	143/10	4/3	29/3	155/8
Hair sparse	3179/39	4663/47	3028/48	5312/54
Hair wet	0/0	0/0	9/3	12/2
Laceration	2/1	0/0	1/1	12/1

+ Number of times observed/Total number of animals affected

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Detailed Clinical Observations[+] - FEMALE

Weeks 1 to 101

Observation	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Pelage/Skin				
Nodule, 1-5 mm	91/8	312/25	181/18	88/11
Nodule, 5-20 mm	2/1	58/6	13/3	17/3
Piloerection	14/7	13/7	4/4	5/2
Scabbed area	227/18	141/20	69/11	163/17
Skin cold to touch	0/0	0/0	2/2	2/2
Skin discolored, Black	1/1	6/1	13/1	2/1
Skin discolored, Blue	15/3	2/1	0/0	0/0
Skin discolored, Brown	4/1	0/0	0/0	0/0
Skin discolored, Pale	0/0	0/0	1/1	0/0
Ulcer, 5-20 mm	0/0	0/0	1/1	0/0
Ulcer plantar/palmar, 1-5 mm	0/0	6/2	27/2	0/0
Unkempt appearance	0/0	9/3	0/0	13/2
Respiration				
Breathing audible	0/0	6/5	1/1	3/1
Breathing difficult	0/0	3/2	2/2	0/0
Breathing rapid	1/1	0/0	0/0	0/0
Breathing shallow	1/1	3/2	3/3	1/1
Breathing slow	0/0	2/2	1/1	0/0
Material in nares	0/0	0/0	1/1	0/0

+ Number of times observed/Total number of animals affected

Table 3
Summary of Mass Findings

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Mass Findings+ - MALE
Weeks 1 to 103

Observation	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Observed	80	80	80	80
Number of Normal Animals	74	74	71	71
Mass				
Abdominal region, Large >or=4 cm	0/0	0/0	0/0	5/1
Abdominal region, Medium 2-3.9 cm	0/0	0/0	0/0	1/1
Anogenital region, Large >or=4 cm	0/0	9/1	0/0	0/0
Anogenital region, Medium 2-3.9 cm	0/0	5/1	0/0	0/0
Axillary region/left, Large >or=4 cm	12/1	0/0	0/0	1/1
Axillary region/left, Mass > 10cm	2/1	0/0	0/0	1/1
Axillary region/left, Medium 2-3.9 cm	2/1	0/0	0/0	7/1
Axillary region/left, Small 1-1.9 cm	0/0	0/0	0/0	10/2
Axillary region/left, Ulcerated, large >or=4 cm	1/1	0/0	0/0	0/0
Axillary region/right, Large >or=4 cm	26/1	0/0	0/0	27/2
Axillary region/right, Medium 2-3.9 cm	39/4	0/0	1/1	29/3
Axillary region/right, Small 1-1.9 cm	12/4	0/0	6/1	7/2
Cervical region, Large >or=4 cm	0/0	8/2	0/0	0/0
Cervical region, Medium 2-3.9 cm	0/0	9/3	2/1	0/0
Cervical region, Small 1-1.9 cm	0/0	6/2	1/1	0/0
Cranial region, Medium 2-3.9 cm	0/0	0/0	2/1	0/0
Cranial region, Small 1-1.9 cm	0/0	0/0	1/1	0/0
Dorsal surface, Large >or=4 cm	0/0	1/1	7/1	0/0
Dorsal surface, Mass > 10cm	0/0	1/1	0/0	0/0

+ Number of times observed/Total number of animals affected

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Mass Findings+ - MALE
Weeks 1 to 103

Observation	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Mass				
Dorsal surface, Medium 2-3.9 cm	0/0	3/1	0/0	0/0
Hind limb/left, Large >or=4 cm	0/0	0/0	0/0	2/1
Hind limb/left, Mass > 10cm	0/0	0/0	0/0	2/1
Hind limb/left, Medium 2-3.9 cm	0/0	0/0	0/0	1/1
Hind limb/left, Small 1-1.9 cm	0/0	0/0	0/0	4/1
Inguinal region/left, Medium 2-3.9 cm	0/0	2/1	0/0	0/0
Inguinal region/left, Small 1-1.9 cm	0/0	1/1	0/0	0/0
Inguinal region/right, Medium 2-3.9 cm	0/0	0/0	1/1	0/0
Inguinal region/right, Small 1-1.9 cm	0/0	0/0	3/1	4/1
Thoracic region, BI Medium Ulcerated 2-4cm	0/0	0/0	1/1	0/0
Thoracic region, Large >or=4 cm	11/1	0/0	4/1	2/1
Thoracic region, Medium 2-3.9 cm	5/1	0/0	3/2	3/1
Thoracic region, Small 1-1.9 cm	0/0	0/0	12/3	0/0

+ Number of times observed/Total number of animals affected

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Mass Findings[+] - FEMALE

Weeks 1 to 103

Observation	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Observed	80	80	80	80
Number of Normal Animals	40	42	45	50
Mass				
Abdominal region, Large >or=4 cm	0/0	0/0	5/1	1/1
Abdominal region, Medium 2-3.9 cm	0/0	0/0	3/1	6/2
Abdominal region, Small 1-1.9 cm	0/0	4/1	2/1	8/3
Anogenital region, Large >or=4 cm	24/4	16/2	10/2	3/1
Anogenital region, Mass > 10cm	1/1	2/1	0/0	0/0
Anogenital region, Medium 2-3.9 cm	119/8	36/7	20/4	22/5
Anogenital region, Small 1-1.9 cm	62/10	81/14	34/4	68/6
Anogenital region, Ulcerated, large >or=4 cm	1/1	0/0	0/0	0/0
Anogenital region, Ulcerated, medium 2-3.9 cm	0/0	3/3	0/0	3/3
Anogenital region, Ulcerated, small 1-1.9 cm	0/0	1/1	0/0	0/0
Axillary region/left, Large >or=4 cm	3/1	2/1	19/2	0/0
Axillary region/left, Medium 2-3.9 cm	24/4	33/3	18/3	4/1
Axillary region/left, Small 1-1.9 cm	62/7	130/11	24/5	23/2
Axillary region/left, Ulcerated, medium 2-3.9 cm	0/0	0/0	1/1	0/0
Axillary region/left, Ulcerated, small 1-1.9 cm	0/0	1/1	1/1	0/0
Axillary region/right, Large >or=4 cm	13/2	10/1	11/2	21/3
Axillary region/right, Mass > 10cm	1/1	0/0	0/0	0/0
Axillary region/right, Medium 2-3.9 cm	34/6	27/4	14/4	19/3
Axillary region/right, Small 1-1.9 cm	94/11	94/11	58/10	58/6

+ Number of times observed/Total number of animals affected

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Mass Findings[+] - FEMALE

Weeks 1 to 103

Observation	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Mass				
Axillary region/right, Ulcerated, large >or=4 cm	0/0	0/0	0/0	2/2
Axillary region/right, Ulcerated, medium 2-3.9 cm	2/2	1/1	0/0	0/0
Axillary region/right, Ulcerated, small 1-1.9 cm	1/1	3/3	2/2	2/2
Cervical region, Large >or=4 cm	13/1	21/1	14/3	14/1
Cervical region, Medium 2-3.9 cm	26/3	8/2	50/6	17/2
Cervical region, Small 1-1.9 cm	58/6	28/4	93/7	11/3
Cervical region, Ulcerated, large >or=4 cm	0/0	0/0	2/2	0/0
Cervical region, Ulcerated, medium 2-3.9 cm	0/0	0/0	2/1	0/0
Face, Ulcerated, small 1-1.9 cm	1/1	0/0	0/0	0/0
Inguinal region/left, Large >or=4 cm	17/3	57/4	0/0	15/4
Inguinal region/left, Mass > 10cm	1/1	11/1	0/0	0/0
Inguinal region/left, Medium 2-3.9 cm	67/10	22/5	0/0	43/7
Inguinal region/left, Small 1-1.9 cm	85/12	40/7	27/3	43/7
Inguinal region/left, Ulcerated, large >or=4 cm	1/1	0/0	0/0	0/0
Inguinal region/left, Ulcerated, medium 2-3.9 cm	1/1	0/0	0/0	3/3
Inguinal region/left, Ulcerated, small 1-1.9 cm	0/0	0/0	0/0	1/1
Inguinal region/right, Large >or=4 cm	11/1	21/1	14/2	0/0
Inguinal region/right, Mass > 10cm	0/0	1/1	0/0	0/0
Inguinal region/right, Medium 2-3.9 cm	24/3	47/6	23/3	13/3
Inguinal region/right, Small 1-1.9 cm	42/6	36/6	29/7	33/5
Inguinal region/right, Ulcerated, medium 2-3.9 cm	0/0	1/1	1/1	0/0
Inguinal region/right, Ulcerated, small 1-1.9 cm	1/1	0/0	0/0	0/0
Lumbar region, Medium 2-3.9 cm	1/1	0/0	0/0	0/0

+ Number of times observed/Total number of animals affected

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Mass Findings+ - FEMALE

Weeks 1 to 103

Observation	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Mass				
Thoracic region, Large >or=4 cm	22/3	0/0	18/2	0/0
Thoracic region, Mass > 10cm	1/1	0/0	0/0	0/0
Thoracic region, Medium 2-3.9 cm	30/2	0/0	24/3	0/0
Thoracic region, Small 1-1.9 cm	36/5	12/2	16/2	5/2
Thoracic region, Ulcerated, medium 2-3.9 cm	0/0	0/0	0/0	1/1

+ Number of times observed/Total number of animals affected

Table 4
Summary of Body Weight Values

Summary of Body Weight Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight g													
	1	237.0	10.92	79	232.5	18.35	80	236.7	11.66	80	237.4	14.78	80
	2	297.6	15.02	79	293.2	20.91	80	299.9	16.75	80	302.2	16.73	80
	3	349.8	19.85	80	346.2	23.00	80	353.3	22.05	80	351.9	20.55	80
	4	394.8	25.90	80	393.3	26.95	79	400.6	26.63	80	392.3	26.29	80
	5	432.7	31.17	80	430.1	31.47	79	435.0	29.85	80	422.1	30.58	80
	6	465.9	34.67	80	463.5	36.60	79	471.5	34.89	80	454.9	37.07	80
	7	489.7	38.22	80	486.6	38.74	79	493.2	36.96	80	473.8[a]	39.19	80
	8	513.6	41.75	80	512.6	43.04	79	517.4	41.41	80	495.5[a]	41.83	80
	9	531.1	45.22	80	530.7	45.41	79	534.8	43.10	80	510.7[a]	45.10	80
	10	549.0	45.84	80	546.8	46.08	79	553.3	45.42	80	528.7[a]	46.73	80
	11	565.8	49.81	80	566.8	49.71	79	569.8	47.36	80	544.7[a]	47.10	80
	12	576.4	50.30	80	577.6	51.49	79	582.5	49.54	80	553.3[a]	52.50	80
	13	589.0	52.68	80	589.4	54.63	79	593.4	53.55	80	563.3[b]	51.29	80
	14	600.7	55.22	80	602.5	56.62	78	607.6	55.13	80	578.8[a]	53.03	80
	16	622.3	60.72	80	624.5	60.87	78	628.1	57.87	80	599.1[a]	55.19	80
	18	645.5	64.53	80	647.1	64.20	78	650.8	63.04	80	619.3[a]	57.92	80
	20	665.4	66.91	80	663.2	68.18	78	668.3	66.52	80	637.1[a]	62.32	80
	22	683.3	70.82	80	682.4	71.58	77	687.5	71.50	80	653.0[a]	64.09	80
	24	697.8	74.60	80	695.0	74.65	77	701.9	74.47	80	664.1[b]	66.41	80
	26	715.6	79.35	80	709.2	76.58	77	713.7	80.01	80	676.8[b]	70.74	80
	28	730.4	81.25	80	722.9	78.87	77	732.0	82.13	80	689.5[b]	70.04	80
	30	744.7	83.35	78	737.6	81.76	77	746.2	85.91	80	706.3[b]	70.97	80

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)
[b] Significantly different from control; (p<0.01)

Summary of Body Weight Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight g													
	32	761.1	86.59	78	748.7	82.27	77	756.3	89.45	79	721.1[b]	75.21	80
	34	771.3	87.81	78	766.4	86.03	77	772.2	93.54	79	734.2[a]	75.72	80
	36	783.2	92.06	78	772.2	87.65	77	777.3	96.37	79	742.2[a]	75.29	80
	38	795.8	90.18	78	784.2	91.27	76	793.8	99.25	78	752.8[b]	76.82	80
	40	805.6	94.23	78	794.7	92.72	76	802.9	100.51	77	763.5[a]	76.53	80
	42	815.8	95.02	78	808.0	94.71	76	807.7	102.02	77	768.4[b]	76.31	80
	44	821.1	97.16	77	812.8	95.24	75	814.7	107.55	77	777.7[a]	77.11	80
	46	823.8	93.84	76	817.0	93.08	75	830.6	107.88	74	785.3[a]	78.58	80
	48	826.8	95.24	76	825.2	94.46	74	836.6	112.99	74	790.5[a]	79.80	79
	50	841.1	97.89	76	834.2	96.62	72	845.5	115.89	74	797.2[a]	86.84	79
	52	842.8	100.18	76	840.5	100.49	71	854.8	109.82	73	808.0	86.03	77
	54	831.9	101.69	66	851.0	99.22	61	868.0	115.04	62	805.4	89.03	67
	56	847.2	91.83	65	864.6	103.16	61	875.1	116.68	62	816.3	88.81	65
	58	853.9	90.29	64	874.7	104.53	59	889.0	118.03	61	819.4	98.99	63
	60	860.3	92.89	63	877.8	107.09	57	891.3	124.65	58	826.2	99.37	59
	62	862.8	98.18	63	882.6	107.68	57	890.5	121.28	56	822.6	110.91	57
	64	878.1	88.62	61	887.7	106.00	56	900.3	123.88	56	835.8	108.92	55
	66	876.4	90.58	60	895.7	108.08	55	899.7	123.60	54	844.5	98.19	52
	68	878.6	90.05	59	891.6	111.03	55	891.9	124.71	52	846.3	102.95	51
	70	880.4	91.45	56	901.1	112.13	55	902.7	130.93	48	855.4	101.96	51
	72	887.1	94.53	55	901.2	114.09	55	910.8	132.82	47	855.3	108.80	50
	74	890.1	96.58	53	898.1	116.76	53	907.1	131.29	46	860.2	106.76	49

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)
[b] Significantly different from control; (p<0.01)

Summary of Body Weight Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight g													
	76	883.0	107.39	52	904.8	114.89	52	911.4	131.03	45	870.0	111.84	49
	78	879.3	120.53	51	899.7	119.11	50	892.0	129.82	42	865.1	115.71	49
	80	885.0	110.87	48	896.9	124.54	49	889.9	133.72	37	868.2	122.24	46
	82	884.4	120.03	48	889.7	130.02	49	887.9	133.92	36	867.6	131.10	45
	84	888.8	113.26	46	879.6	142.39	47	894.5	140.97	34	878.0	128.37	42
	86	884.2	128.30	45	898.2	131.68	44	896.9	138.22	33	876.0	141.62	40
	88	896.0	131.42	41	902.1	130.50	43	868.7	128.58	31	886.1	126.69	37
	90	876.8	111.92	36	902.5	136.75	41	856.3	140.84	29	901.9	109.44	32
	92	874.0	121.65	34	901.7	137.43	36	847.3	131.71	26	899.3	119.18	30
	94	877.1	121.42	31	916.9	135.18	30	836.8	140.32	26	895.8	118.27	28
	96	865.4	131.55	28	899.2	136.70	28	843.9	135.49	24	898.5	114.34	28
	98	852.6	126.22	26	895.4	134.67	28	823.6	129.72	23	884.3	105.62	26
	100	825.2	137.19	21	874.7	140.18	26	803.2	135.59	21	881.7	108.46	26
	102	820.8	141.50	19	839.5	168.66	24	788.4	136.51	20	860.1	111.05	25
	104	812.9	154.30	17	860.4	160.85	20	771.6	140.05	19	856.1	99.88	18

N - Number of measures used to calculate mean
SD - Standard Deviation

Summary of Body Weight Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight g													
	1	168.6	10.77	80	165.6	9.63	80	166.6	11.32	80	168.0	11.60	80
	2	192.2	13.99	80	188.1	11.22	80	191.4	12.73	80	194.5	13.61	80
	3	213.5	16.61	80	209.6	12.77	80	213.9	15.26	80	218.1	15.56	80
	4	233.5	19.84	80	226.3[a]	16.53	80	232.6	16.88	80	236.3	17.27	80
	5	246.9	22.03	80	236.2[b]	19.51	80	243.1	20.05	80	249.5	17.89	80
	6	260.1	23.59	80	251.4[a]	19.95	80	257.9	21.56	80	265.6	19.20	80
	7	265.6	25.44	80	256.4[a]	20.19	80	264.1	22.11	80	271.7	19.58	80
	8	275.2	26.25	80	266.3[a]	21.04	80	272.8	22.88	80	279.5	20.01	80
	9	280.2	27.11	80	273.3	21.61	80	278.5	23.82	80	286.9	20.56	80
	10	283.9	28.24	80	277.1	22.07	80	283.2	24.20	80	291.6	21.06	80
	11	292.2	30.65	80	283.5	22.56	80	290.7	24.87	80	297.1	21.87	80
	12	297.9	31.51	80	288.9	23.32	80	296.4	26.30	80	301.4	23.04	80
	13	302.9	33.32	80	290.7[a]	24.85	80	302.1	25.87	80	304.2	24.68	80
	14	308.3	33.41	80	299.2	26.06	80	305.9	26.24	80	312.2	25.24	80
	16	316.5	35.94	80	306.2	27.82	80	313.8	28.29	80	314.8	27.22	80
	18	325.0	36.15	80	315.0	29.00	80	324.4	30.36	80	325.9	27.89	80
	20	331.8	37.09	80	322.1	32.07	80	335.6	30.18	80	335.0	31.13	80
	22	341.2	37.80	80	331.4	34.10	80	343.2	31.02	80	340.6	32.61	80
	24	346.8	40.84	80	333.0[a]	37.08	80	350.3	32.44	80	342.8	34.05	80
	26	356.3	41.93	80	341.5[a]	38.32	80	359.1	35.85	79	350.0	36.80	80
	28	366.1	45.98	80	350.9	39.71	80	365.5	37.40	79	351.7	40.82	80
	30	375.0	48.56	80	359.1	43.72	80	373.5	39.10	79	356.7[a]	41.73	79

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)
[b] Significantly different from control; (p<0.01)

Summary of Body Weight Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight g													
	32	387.4	53.04	80	367.8[a]	45.43	79	387.1	42.29	79	363.4[b]	43.99	79
	34	395.0	53.17	80	376.6[a]	47.69	79	394.1	43.94	79	371.6[b]	45.48	79
	36	402.5	57.09	80	379.8[a]	47.80	79	399.9	46.32	79	371.7[b]	47.45	79
	38	415.2	59.01	79	389.6[b]	50.84	79	411.8	48.24	79	376.7[b]	50.20	79
	40	425.8	61.64	79	395.8[b]	53.70	79	415.7	49.98	78	381.6[b]	51.30	79
	42	430.8	63.81	79	401.2[b]	54.73	78	424.2	51.10	77	385.7[b]	54.24	79
	44	434.6	64.45	79	410.9[a]	56.06	77	428.9	51.56	77	393.3[b]	55.74	79
	46	439.5	67.65	78	417.8	56.09	77	436.1	54.66	77	394.9[b]	59.71	79
	48	451.6	70.22	78	422.4[b]	55.84	77	442.3	57.01	74	398.6[b]	59.08	78
	50	459.8	73.49	77	431.0[a]	58.52	77	451.2	58.97	74	406.8[b]	61.01	78
	52	470.1	73.27	74	435.2[b]	59.52	77	461.3	64.06	73	407.5[b]	63.59	75
	54	461.7	75.04	63	435.3	58.18	66	455.0	66.46	62	415.2[b]	62.13	65
	56	477.6	78.37	62	442.2[a]	63.01	65	466.7	71.44	61	423.0[b]	66.37	65
	58	482.2	76.22	61	451.2[a]	66.64	65	485.4	61.64	58	428.6[b]	61.95	62
	60	487.1	74.39	59	460.0	65.13	63	487.8	59.54	58	425.1[b]	64.42	59
	62	483.9	77.33	59	458.0	66.46	62	482.8	61.36	57	429.3[b]	65.43	59
	64	487.6	78.67	58	464.7	68.06	60	492.5	68.11	55	437.7[b]	67.33	59
	66	490.2	84.55	56	471.5	62.37	59	498.7	71.14	53	440.5[b]	68.13	59
	68	493.0	82.35	51	473.7	64.35	59	508.8	64.93	51	435.5[b]	69.70	58
	70	495.1	87.10	49	477.3	66.28	58	515.6	60.88	50	451.0[b]	74.00	56
	72	507.4	92.42	47	483.1	68.81	58	514.2	63.27	49	449.0[b]	76.50	56
	74	518.9	90.86	45	482.8	73.72	56	517.4	66.49	49	458.7[b]	81.41	55

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)
[b] Significantly different from control; (p<0.01)

Summary of Body Weight Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight g													
	76	529.5	95.31	44	479.9[b]	78.07	53	519.5	71.16	45	457.8[b]	76.07	52
	78	524.2	91.05	43	467.9[b]	81.94	53	520.4	68.05	43	452.8[b]	80.81	50
	80	513.0	91.20	42	473.9	75.29	47	517.1	69.13	39	450.4[b]	86.62	49
	82	522.0	92.74	41	482.1	78.35	44	528.5	63.33	35	445.8[b]	77.35	47
	84	518.7	94.08	41	489.9	82.40	42	533.2	70.44	34	447.7[b]	82.97	44
	86	516.3	99.37	41	480.9	85.74	41	539.9	81.44	32	460.6[a]	84.69	37
	88	496.1	80.49	35	483.9	74.02	35	550.2[a]	79.78	31	455.7	91.62	34
	90	493.7	80.47	30	484.8	77.00	32	528.4	60.78	24	459.4	89.99	31
	92	490.7	84.10	28	493.7	76.20	28	526.7	67.91	22	469.9	84.85	25
	94	477.6	86.78	25	493.5	88.19	26	519.8	72.61	20	474.4	95.51	24
	96	476.4	88.02	21	499.2	89.68	25	532.6	69.20	18	482.7	94.82	24
	98	490.8	76.41	18	493.5	98.85	24	537.4	77.30	17	477.8	94.64	20
	100	489.7	75.26	17	503.7	94.59	22	539.5	73.47	17	472.7	91.36	19

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)
[b] Significantly different from control; (p<0.01)

Table 5
Summary of Body Weight Change Values

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Body Weight Change Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change g													
	(-2)-1	94.8	8.47	79	90.4	17.28	80	94.9	8.67	80	95.9	12.11	80
	1-2	60.6	6.34	79	60.7	8.24	80	63.2	7.37	80	64.8[b]	9.51	80
	2-3	51.7	8.06	79	53.0	9.28	80	53.4	8.13	80	49.7	10.14	80
	3-4	45.1	10.00	80	47.1	8.16	79	47.2	7.67	80	40.4[b]	8.53	80
	4-5	37.9	7.94	80	36.8	8.43	79	34.4[a]	7.51	80	29.8[b]	7.83	80
	5-6	33.2	7.98	80	33.4	9.10	79	36.5	8.95	80	32.8	12.81	80
	6-7	23.8	6.56	80	23.0	6.27	79	21.7	6.37	80	18.9[b]	8.45	80
	7-8	23.9	6.31	80	26.1	7.77	79	24.2	8.55	80	21.8	7.55	80
	8-9	17.5	7.03	80	18.1	6.12	79	17.4	9.98	80	15.2	9.15	80
	9-10	17.9	6.48	80	16.1	7.20	79	18.5	8.14	80	17.9	6.97	80
	10-11	16.8	7.87	80	19.9[a]	8.45	79	16.5	6.19	80	16.1	6.16	80
	11-12	10.6	8.54	80	10.8	6.13	79	12.7	6.97	80	8.6	12.34	80
	12-13	12.6	9.57	80	11.8	8.74	79	10.9	10.18	80	10.0	10.30	80
	13-14	11.7	8.06	80	13.1	7.04	78	14.3	7.54	80	15.6[b]	8.59	80
	14-16	21.6	12.48	80	22.0	9.55	78	20.5	8.71	80	20.3	8.44	80
	16-18	23.3	9.85	80	22.7	9.38	78	22.7	9.03	80	20.2	8.84	80
	18-20	19.8	8.53	80	16.0[a]	8.90	78	17.5	6.99	80	17.8	9.20	80
	20-22	17.9	9.66	80	19.8	7.29	77	19.2	9.00	80	16.0	10.52	80
	22-24	14.6	10.18	80	12.7	8.72	77	14.4	9.87	80	11.1	10.15	80
	24-26	17.8	9.22	80	14.1	9.12	77	11.9[b]	14.07	80	12.7[a]	12.22	80
	26-28	14.8	11.22	80	13.7	12.28	77	18.2	12.36	80	12.7	13.58	80
	28-30	13.7	8.74	78	14.7	9.17	77	14.2	11.05	80	16.8	13.05	80

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)
[b] Significantly different from control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Body Weight Change Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change g													
	30-32	16.4	8.17	78	11.1[b]	9.16	77	11.2[b]	10.76	79	14.8	11.91	80
	32-34	10.2	7.97	78	17.6[b]	10.34	77	15.9[b]	10.60	79	13.2	9.73	80
	34-36	11.9	9.74	78	5.9[b]	11.97	77	5.1[b]	10.78	79	8.0	10.42	80
	36-38	12.6	13.97	78	11.0	11.54	76	16.2	12.13	78	10.6	10.42	80
	38-40	9.8	9.89	78	10.5	9.60	76	7.4	12.36	77	10.7	10.28	80
	40-42	10.2	9.32	78	13.2	10.10	76	4.8[a]	17.57	77	5.0[a]	15.30	80
	42-44	5.6	8.54	77	6.0	8.51	75	7.0	19.17	77	9.3	10.41	80
	44-46	6.3	8.72	76	4.1	11.28	75	11.3[b]	11.72	74	7.7	9.61	80
	46-48	3.0	13.39	76	10.6[b]	11.65	74	6.0	13.08	74	6.2	10.17	79
	48-50	14.3	14.06	76	9.1	17.40	72	8.9	10.78	74	6.6[a]	21.68	79
	50-52	1.7	18.33	76	5.4	11.49	71	4.5	15.20	73	6.3	16.07	77
	52-54	-6.5	22.85	66	6.4[b]	10.38	61	3.2[b]	17.12	62	1.3[a]	17.95	67
	54-56	10.7	22.27	65	13.6	12.43	61	7.2	12.77	62	9.7	15.73	65
	56-58	5.4	17.85	64	6.4	15.59	59	13.5[a]	16.08	61	4.6	21.31	63
	58-60	6.7	25.53	63	2.0	18.21	57	-0.7	20.36	58	9.2	14.47	59
	60-62	2.6	20.70	63	4.9	10.94	57	-3.8	16.91	56	-3.6	21.66	57
	62-64	7.1	16.56	61	8.0	12.86	56	9.8	14.87	56	4.0	25.56	55
	64-66	-4.1	25.33	60	5.5[a]	12.19	55	0.7	16.24	54	0.9	22.17	52
	66-68	-0.7	22.26	59	-4.1	20.89	55	-5.5	22.02	52	4.4	13.11	51
	68-70	-0.6	17.74	56	9.5[b]	19.11	55	10.1[b]	15.29	48	9.0[a]	14.38	51
	70-72	8.2	20.90	55	0.1	25.50	55	9.1	11.43	47	1.1	18.97	50
	72-74	3.4	19.22	53	1.4	24.38	53	-5.5	23.84	46	6.2	15.33	49

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)
[b] Significantly different from control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Body Weight Change Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change g													
	74-76	-6.6	35.69	52	3.1	20.95	52	5.8	24.75	45	9.8[b]	17.65	49
	76-78	-2.9	24.89	51	-3.4	18.49	50	-8.1	24.23	42	-4.9	27.55	49
	78-80	-3.6	21.00	48	-3.1	15.77	49	-7.5	39.54	37	-4.2	27.25	46
	80-82	-0.6	26.30	48	-7.1	27.88	49	-4.1	24.39	36	-3.9	25.88	45
	82-84	-7.0	26.98	46	-7.9	36.67	47	1.9	29.28	34	-3.2	31.56	42
	84-86	-5.4	40.88	45	1.0	21.55	44	0.0	22.85	33	-11.4	42.84	40
	86-88	-3.0	38.38	41	-1.7	11.94	43	-16.4	30.61	31	-9.2	28.50	37
	88-90	-8.4	24.71	36	0.3	29.04	41	-14.4	43.33	29	2.0	10.45	32
	90-92	-8.4	26.79	34	-11.9	34.99	36	-11.4	28.51	26	-1.5	19.35	30
	92-94	-11.5	23.34	31	-6.1	25.32	30	-10.5	27.06	26	0.4	18.39	28
	94-96	-14.4	31.29	28	-15.7	31.24	28	-10.5	20.01	24	2.7[a]	17.16	28
	96-98	-25.4	33.59	26	-3.8[a]	29.70	28	-11.8	22.19	23	0.4[b]	22.19	26
	98-100	-17.0	25.22	21	-24.9	39.47	26	-20.7	30.82	21	-2.7	28.50	26
	100-102	-12.4	26.95	19	-30.9	53.54	24	-15.7	28.76	20	-14.8	28.88	25
	102-104	-22.0	34.99	17	-13.8	21.27	20	-25.2	24.00	19	-15.4	28.22	18

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)
[b] Significantly different from control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Body Weight Change Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change g													
	(-2)-1	55.3	9.42	80	52.3	8.83	80	53.2	9.46	80	54.5	9.79	80
	1-2	23.6	6.81	80	22.5	5.47	80	24.8	5.76	80	26.5[b]	5.01	80
	2-3	21.3	6.82	80	21.5	5.09	80	22.5	5.76	80	23.6[a]	5.30	80
	3-4	20.0	6.76	80	16.7[a]	10.64	80	18.8	6.38	80	18.3	5.62	80
	4-5	13.4	5.68	80	9.9	12.40	80	10.4[b]	6.02	80	13.2	4.42	80
	5-6	13.2	5.37	80	15.2	8.84	80	14.9	5.41	80	16.1[b]	6.29	80
	6-7	5.4	6.39	80	5.0	6.37	80	6.2	5.21	80	6.0	5.26	80
	7-8	9.6	5.03	80	9.9	5.32	80	8.7	6.00	80	7.8	5.05	80
	8-9	5.1	5.80	80	7.0	5.39	80	5.7	4.38	80	7.5[a]	5.68	80
	9-10	3.6	6.29	80	3.8	5.89	80	4.7	5.67	80	4.6	4.90	80
	10-11	8.3	6.22	80	6.4	5.83	80	7.5	6.06	80	5.6[b]	4.98	80
	11-12	5.8	5.33	80	5.4	5.08	80	5.7	8.70	80	4.3	5.16	80
	12-13	5.0	8.52	80	1.8[a]	5.93	80	5.7	9.30	80	2.8	5.79	80
	13-14	5.4	7.29	80	8.4[a]	6.51	80	3.8	7.37	80	8.0[a]	6.49	80
	14-16	8.1	8.42	80	7.1	6.17	80	7.9	7.45	80	2.6[b]	7.74	80
	16-18	8.6	7.69	80	8.8	6.22	80	10.6	6.87	80	11.1[a]	5.95	80
	18-20	6.8	10.51	80	7.1	7.45	80	11.2[b]	7.30	80	9.2	6.70	80
	20-22	9.4	7.67	80	9.3	8.11	80	7.6	9.28	80	5.6[b]	7.70	80
	22-24	5.6	8.78	80	1.6[a]	11.59	80	7.1	6.77	80	2.2[a]	7.67	80
	24-26	9.5	8.68	80	8.5	8.84	80	8.6	6.70	79	7.2	7.17	80
	26-28	9.8	9.11	80	9.4	10.10	80	6.4	8.27	79	1.8[b]	9.83	80
	28-30	8.9	8.59	80	8.2	8.64	80	8.0	8.06	79	6.1	7.51	79

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)
[b] Significantly different from control; (p<0.01)

Summary of Body Weight Change Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change g													
	30-32	12.4	9.55	80	9.7	7.73	79	13.6	7.07	79	6.7[b]	7.83	79
	32-34	7.6	8.09	80	8.8	7.61	79	7.0	6.63	79	8.2	7.88	79
	34-36	7.5	10.35	80	3.2[a]	11.35	79	5.8	7.28	79	0.1[b]	7.60	79
	36-38	12.1	10.96	79	9.8	12.37	79	11.9	8.58	79	5.0[b]	7.52	79
	38-40	10.5	7.82	79	6.2[b]	8.76	79	3.4[b]	6.86	78	4.9[b]	6.19	79
	40-42	5.0	8.31	79	4.5	8.86	78	7.9	6.89	77	4.1	11.90	79
	42-44	3.8	8.59	79	8.9[b]	8.60	77	4.8	10.49	77	7.6[a]	11.51	79
	44-46	5.5	9.66	78	6.9	8.35	77	7.2	10.67	77	1.6[a]	10.27	79
	46-48	12.2	10.48	78	4.6[b]	7.64	77	7.3[b]	8.42	74	1.9[b]	8.93	78
	48-50	10.0	15.51	77	8.6	9.54	77	8.9	10.25	74	8.1	9.57	78
	50-52	8.3	11.73	74	4.2	10.78	77	9.1	16.92	73	3.5	9.49	75
	52-54	-4.3	11.77	63	-1.2	11.11	66	-5.4	17.25	62	2.6[b]	11.24	65
	54-56	14.9	10.32	62	7.8[b]	15.03	65	9.5[a]	12.79	61	7.8[b]	11.52	65
	56-58	8.4	11.41	61	9.0	12.98	65	10.0	7.82	58	1.4[b]	14.68	62
	58-60	6.8	10.64	59	5.7	13.15	63	2.4	20.03	58	-2.8[b]	11.30	59
	60-62	-3.2	13.31	59	-2.6	8.72	62	-5.5	21.51	57	4.2[a]	8.13	59
	62-64	1.4	19.99	58	8.1[a]	8.85	60	7.7	17.25	55	8.3[a]	11.38	59
	64-66	0.5	21.68	56	3.6	10.00	59	4.4	12.15	53	2.9	12.55	59
	66-68	-1.2	18.83	51	2.2	9.74	59	4.5	11.08	51	-5.1	13.33	58
	68-70	3.1	19.04	49	5.6	23.83	58	4.7	17.91	50	13.1[a]	10.69	56
	70-72	9.3	10.38	47	5.8	13.20	58	0.0[b]	18.22	49	-1.9[b]	9.85	56
	72-74	4.2	12.97	45	-1.8	18.08	56	3.2	18.98	49	8.0	19.78	55

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)
[b] Significantly different from control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Body Weight Change Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change g													
	74-76	7.6	12.69	44	-7.3[b]	22.61	53	0.7	14.89	45	2.0	19.13	52
	76-78	-8.6	12.55	43	-11.9	20.11	53	-4.0	19.75	43	-2.2	15.20	50
	78-80	-8.0	10.99	42	-8.8	19.82	47	-6.1	15.20	39	-3.8	17.59	49
	80-82	7.4	8.73	41	2.3	13.90	44	-0.5[a]	17.66	35	-1.9[b]	10.62	47
	82-84	-3.2	15.02	41	2.4	19.74	42	2.4	27.21	34	6.3	19.14	44
	84-86	-2.4	22.85	41	-4.5	20.19	41	3.4	19.99	32	3.8	8.88	37
	86-88	-11.1	21.44	35	1.5[b]	12.79	35	4.3[b]	17.28	31	-5.6	18.67	34
	88-90	-9.5	24.70	30	1.0	11.58	32	1.1	13.29	24	3.8[a]	18.98	31
	90-92	-7.8	23.68	28	2.8	12.04	28	-2.4	17.78	22	-2.0	18.39	25
	92-94	-9.1	29.89	25	-0.8	28.68	26	-10.5	28.19	20	6.4	16.38	24
	94-96	-7.6	19.81	21	2.2	17.89	25	-0.5	19.46	18	8.3[b]	12.20	24
	96-98	-7.1	29.14	18	-2.8	17.87	24	0.5	18.35	17	1.5	10.67	20
	98-100	-6.7	23.15	17	-4.7	20.60	22	2.1	17.11	17	-0.4	10.01	19

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)
[b] Significantly different from control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Body Weight Change Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change g	1-13	351.9	47.30	79	356.8	51.76	79	356.7	47.87	80	325.9[b]	44.15	80

N - Number of measures used to calculate mean
SD - Standard Deviation

[b] Significantly different from control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Body Weight Change Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change g	1-13	134.3	26.76	80	125.1[a]	22.49	80	135.5	20.48	80	136.2	19.99	80

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Body Weight Change Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change g	1-52	605.6	96.21	75	608.0	97.19	71	617.8	105.12	73	570.2	81.77	77

N - Number of measures used to calculate mean
SD - Standard Deviation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Body Weight Change Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change g	1-52	301.2	68.80	74	269.5[b]	56.71	77	294.2	60.78	73	239.7[b]	61.80	75

N - Number of measures used to calculate mean
SD - Standard Deviation

[b] Significantly different from control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Body Weight Change Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change g	1-104	578.8	156.34	17	634.5	155.46	20	537.4	139.55	19	616.3	99.77	18

N - Number of measures used to calculate mean
SD - Standard Deviation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Body Weight Change Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change g	1-100	322.8	69.93	17	339.2	92.66	22	369.0	74.09	17	304.4	89.28	19

N - Number of measures used to calculate mean
SD - Standard Deviation

Table 6
Summary of Food Consumption Values

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Food Consumption Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day	1-13	29.70	1.497	80	30.06	1.772	79	30.01	2.191	80	30.19	1.693	80

N - Number of measures used to calculate mean
SD - Standard Deviation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Food Consumption Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day	1-52	29.65	1.781	76	29.79	1.808	72	29.83	2.145	74	30.09	1.848	78

N - Number of measures used to calculate mean
SD - Standard Deviation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Food Consumption Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day	1-102	29.13	1.438	17	29.43	1.476	20	29.50	1.964	20	30.83[a]	2.154	23

N - Number of measures used to calculate mean
SD - Standard Deviation

[a]Significantly different from control; ($p<0.05$)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Food Consumption Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day													
	-1	23.67	1.148	79	23.86	1.610	80	23.62	1.215	80	23.93	1.257	79
	1	27.78	1.169	79	27.06	2.637	80	27.42	1.928	80	27.80	2.334	79
	2	29.20	1.213	79	29.51	1.704	80	29.80	1.912	80	30.36[b]	1.804	80
	3	29.32	1.739	80	30.09[a]	1.743	80	29.70	2.097	80	30.49[b]	1.847	80
	4	30.13	1.670	80	30.93[a]	2.127	79	30.71	2.277	78	31.02[b]	1.657	80
	5	29.67	1.872	80	29.42	1.903	79	29.80	2.569	80	29.53	2.489	80
	6	30.07	1.687	80	30.56	2.047	79	30.30	2.197	76	30.42	2.470	80
	7	29.21	1.737	80	29.63	2.193	79	29.08	2.324	80	29.49	2.408	80
	8	29.96	1.754	80	30.72	2.030	79	29.67	2.088	80	30.24	2.428	80
	9	29.81	1.827	80	30.02	1.971	79	29.86	2.009	80	30.08	1.921	80
	10	30.14	2.059	80	31.40[a]	2.148	77	31.78[b]	5.067	80	31.04	1.909	80
	11	30.34	1.777	80	30.67	2.166	79	30.75	3.779	80	30.34	2.355	80
	12	30.63	1.976	80	31.14	1.960	79	30.86	3.665	80	31.03	2.755	80
	13	29.79	1.899	80	29.75	2.128	78	30.11	2.155	80	30.57[a]	2.087	80
	14	30.42	1.988	80	30.46	2.197	78	29.84	2.379	78	30.41	2.033	80
	16	29.69	2.417	80	29.86	2.200	78	29.71	2.299	80	30.58[a]	2.222	80
	18	29.84	1.959	80	29.62	1.937	78	29.33	2.336	80	29.95	2.178	80
	20	29.94	2.135	78	29.60	2.084	38	29.86	2.177	80	30.23	2.180	80
	22	30.03	2.066	80	29.91	1.932	77	29.83	2.414	80	29.82	2.136	80
	24	29.77	2.170	80	28.89[a]	2.164	77	29.31	2.214	80	29.55	2.421	80
	26	29.76	2.181	78	29.61	2.148	77	29.93	2.908	80	30.11	2.589	80
	28	29.37	2.068	79	29.68	2.762	77	29.68	2.406	78	29.49	2.481	80
	30	30.07	2.286	76	29.87	2.289	77	29.56	2.475	79	30.33	2.396	80
	32	29.42	2.282	78	29.89	2.154	71	30.50[a]	2.370	77	30.02	2.379	78

N - Number of measures used to calculate mean
SD - Standard Deviation

[a]Significantly different from control; (p<0.05)
[b]Significantly different from control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Food Consumption Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day													
	34	30.52	2.274	78	30.31	2.786	77	29.58	2.611	77	30.07	2.262	80
	36	29.99	2.496	78	29.68	2.580	77	30.02	2.662	78	30.53	2.250	80
	38	30.09	2.691	78	30.15	2.440	76	29.78	2.305	77	30.18	2.344	80
	40	30.32	2.591	78	29.95	2.379	74	29.99	2.626	77	30.37	2.309	80
	42	29.95	2.456	74	29.95	2.302	76	28.88[a]	2.906	77	29.73	2.556	80
	44	29.24	2.633	77	29.81	1.911	75	29.91	3.033	73	30.44[a]	2.542	80
	46	28.54	2.680	76	28.67	1.836	75	29.60	2.837	73	29.47	2.697	80
	48	29.01	3.035	76	28.59	2.494	73	29.67	3.461	74	29.89	2.758	79
	50	28.70	3.119	76	28.09	3.001	72	29.33	3.158	74	28.93	3.718	79
	52	28.69	3.386	76	29.69	2.780	69	29.94[a]	2.883	72	29.73	2.930	75
	54	28.43	3.327	66	29.61	2.630	61	29.51	2.797	62	29.38	4.147	67
	56	30.02	2.367	64	30.05	2.550	60	30.18	3.241	62	29.50	3.774	65
	58	29.89	3.336	64	30.65	2.980	59	30.94	4.315	60	30.52	3.493	62
	60	29.65	4.380	63	29.79	3.332	55	30.57	4.310	58	30.78	4.028	59
	62	30.07	4.460	63	29.96	4.558	57	29.85	3.668	56	29.69	4.353	57
	64	30.33	2.763	61	31.50	3.465	56	30.35	3.278	56	30.29	3.518	53
	66	30.12	2.893	59	30.95	2.480	54	30.33	3.708	54	30.72	5.151	52
	68	30.99	4.389	58	31.12	3.331	55	30.18	5.716	52	31.93	5.404	51
	70	31.01	5.665	55	31.94	4.562	55	32.16	4.409	48	31.63	6.298	51
	72	29.62	2.893	53	30.58	4.999	53	31.55	4.301	47	31.18	6.319	50
	74	30.30	6.410	51	30.96	3.603	52	30.15	5.103	46	32.11	6.152	49
	76	29.48	7.792	52	31.39	4.289	51	30.50	5.627	45	31.63	6.330	47
	78	31.07	6.814	51	31.72	5.373	50	29.10	4.557	42	30.82	7.495	49
	80	30.89	6.043	48	32.10	5.082	49	29.46	4.986	36	30.80	8.234	46

N - Number of measures used to calculate mean
SD - Standard Deviation

[a]Significantly different from control; ($p<0.05$)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Food Consumption Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day													
	82	30.55	6.648	47	30.87	5.016	48	30.63	4.458	34	31.07	8.086	42
	84	29.12	5.978	46	30.19	5.609	47	29.81	6.273	34	30.18	7.918	41
	86	29.07	6.606	43	30.43	4.626	43	29.58	4.610	33	29.44	6.641	38
	88	29.99	5.281	40	31.02	5.457	43	27.13	6.583	31	29.79	5.925	35
	90	28.96	5.040	36	30.32	5.524	40	27.84	7.261	28	31.01	5.145	32
	92	29.10	6.083	31	27.72	6.032	36	28.54	5.553	25	30.77	6.045	29
	94	28.43	4.737	30	29.59	6.121	30	27.69	5.645	26	30.84	4.590	27
	96	28.36	4.446	27	27.60	4.103	28	28.91	4.054	24	29.96	3.369	27
	98	27.32	5.592	25	27.33	5.168	27	27.64	5.540	22	30.14	5.808	26
	100	28.19	5.302	19	24.88	5.740	24	25.36	5.644	21	28.76	4.860	26
	102	28.13	5.222	18	27.52	5.616	20	26.71	5.940	20	29.42	5.511	23

N - Number of measures used to calculate mean
SD - Standard Deviation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Food Consumption Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day Mean	0 mg/kg/day SD	0 mg/kg/day N	1 mg/kg/day Mean	1 mg/kg/day SD	1 mg/kg/day N	50 mg/kg/day Mean	50 mg/kg/day SD	50 mg/kg/day N	500 mg/kg/day Mean	500 mg/kg/day SD	500 mg/kg/day N
Food Consumption g/animal/day	1-13	19.65	1.527	80	19.09[a]	1.345	80	19.21	1.241	80	20.28[b]	1.167	80

N - Number of measures used to calculate mean
SD - Standard Deviation

[a]Significantly different from control; (p<0.05)
[b]Significantly different from control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Food Consumption Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day	1-52	19.68	1.538	76	18.88[b]	1.392	77	18.90[b]	1.049	73	20.13	1.459	76

N - Number of measures used to calculate mean
SD - Standard Deviation

[b]Significantly different from control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Food Consumption Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day	1-100	19.00	1.352	17	18.74	1.482	22	19.30	1.227	16	19.84	1.987	18

N - Number of measures used to calculate mean
SD - Standard Deviation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Food Consumption Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day													
	-1	18.59	1.149	80	17.84[b]	1.106	80	17.40[b]	0.943	80	18.07[b]	0.976	78
	1	19.21	1.292	80	18.82	1.713	80	19.12	2.620	80	19.15	1.719	80
	2	20.01	1.505	80	19.19[b]	1.318	80	19.79	1.571	80	20.26	1.188	80
	3	20.17	2.872	80	19.47	3.549	80	19.98	3.322	80	20.54	2.101	80
	4	20.47	1.818	78	19.69[b]	1.743	78	19.61[b]	1.495	80	20.78	1.397	80
	5	19.64	1.800	76	18.73[a]	2.211	80	18.81[b]	1.372	80	19.86	1.347	80
	6	20.04	1.697	80	19.42	1.662	80	19.84	2.157	80	20.78[a]	1.273	80
	7	19.01	1.507	80	18.33[b]	1.641	80	18.33[b]	1.428	80	19.71[b]	1.219	80
	8	19.18	1.753	80	19.48	2.951	80	18.82	1.559	80	20.02[a]	1.232	80
	9	19.30	1.817	80	18.76	1.502	80	19.21	1.404	80	20.23[b]	1.838	80
	10	19.43	1.920	80	19.39	1.444	80	19.18	1.549	80	20.76[b]	1.489	80
	11	19.93	3.786	80	19.48	2.195	80	19.41	2.154	80	20.96	1.578	80
	12	19.39	1.644	80	18.74[a]	1.484	80	18.87	1.180	80	20.21[b]	1.494	80
	13	19.68	1.598	80	18.70[b]	1.946	80	18.76[b]	1.379	80	20.41[a]	1.324	80
	14	19.87	1.650	80	19.00[b]	1.616	80	19.19[a]	1.407	80	20.31	1.693	80
	16	18.93	1.602	80	18.01[b]	1.490	80	18.09[b]	1.281	80	19.61[b]	1.283	80
	18	18.93	1.626	80	18.20[b]	1.553	80	18.14[b]	1.296	80	19.84[b]	1.450	80
	20	19.55	3.171	80	18.63[a]	1.760	80	18.87	1.382	80	20.31	1.508	80
	22	19.36	2.447	80	18.53[a]	1.708	80	18.57[a]	1.398	80	20.01	1.804	80
	24	19.35	2.655	80	17.95[b]	1.693	78	18.59[a]	1.449	80	19.93	1.956	80
	26	19.50	1.841	78	19.16	1.926	80	18.79[a]	1.322	79	20.00	1.868	80
	28	19.65	2.038	80	18.73[a]	2.014	78	18.37[b]	1.597	79	19.59	2.173	80
	30	19.90	1.937	80	17.83[b]	2.039	80	18.53[b]	1.313	79	19.83	1.847	79
	32	18.60	2.047	80	20.39[b]	2.063	79	18.94	1.427	79	19.96[b]	1.891	79

N - Number of measures used to calculate mean
SD - Standard Deviation

[a]Significantly different from control; (p<0.05)
[b]Significantly different from control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Food Consumption Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day Mean	0 mg/kg/day SD	0 mg/kg/day N	1 mg/kg/day Mean	1 mg/kg/day SD	1 mg/kg/day N	50 mg/kg/day Mean	50 mg/kg/day SD	50 mg/kg/day N	500 mg/kg/day Mean	500 mg/kg/day SD	500 mg/kg/day N
Food Consumption g/animal/day													
	34	21.44	2.036	80	18.84[b]	1.773	79	18.80[b]	1.527	79	20.25[b]	2.019	79
	36	20.88	2.748	80	19.27[b]	1.958	79	19.09[b]	1.550	79	20.45	2.233	79
	38	20.51	2.312	78	18.83[b]	1.926	79	18.97[b]	1.400	78	20.48	1.975	79
	40	19.97	2.016	79	19.23[a]	1.687	78	19.10[a]	1.523	78	20.35	2.257	79
	42	19.70	1.734	79	18.69[b]	2.206	76	18.71[b]	1.519	77	20.62[a]	2.455	79
	44	19.96	1.919	79	19.29	1.631	77	18.91[b]	1.557	77	20.69	2.465	79
	46	19.63	1.600	78	18.59[b]	1.806	77	18.48[b]	1.875	76	19.61	2.891	76
	48	19.54	2.283	78	18.48[b]	1.569	77	19.19	1.962	74	19.94	2.231	78
	50	18.62	2.587	75	18.51	1.920	77	18.81	2.331	74	19.51	2.741	78
	52	19.61	2.074	74	18.40[b]	1.635	77	18.30[b]	2.589	70	20.29	2.674	75
	54	18.28	1.984	63	17.27[b]	1.682	66	17.39	2.666	62	19.86[b]	3.371	65
	56	19.79	1.734	62	18.14[b]	2.242	65	18.75[a]	2.134	60	20.53	2.580	65
	58	19.92	2.079	61	18.48[b]	2.293	64	19.48	1.534	58	20.12	2.337	61
	60	19.04	2.726	59	18.71	2.481	63	18.35	2.636	58	20.57[b]	2.746	59
	62	19.00	1.906	58	18.14[a]	1.957	62	17.90	3.160	55	20.79[b]	3.476	59
	64	18.55	2.887	58	18.46	2.580	59	18.62	2.746	53	20.33[b]	3.073	59
	66	18.56	3.150	56	18.79	1.731	59	19.29	2.416	53	20.20[a]	2.865	59
	68	19.33	3.380	51	18.94	1.787	59	19.44	1.870	51	20.54	2.622	58
	70	20.12	2.122	48	18.28[b]	2.575	58	19.33	2.323	49	21.24	3.033	56
	72	19.41	2.201	47	18.30[a]	2.207	58	19.46	4.062	49	20.95[a]	3.358	56
	74	19.80	2.544	44	18.03[b]	2.213	56	18.51	3.018	49	21.00	3.356	54
	76	19.57	2.817	42	17.32[b]	2.822	53	18.32	2.674	44	21.03	3.586	52
	78	18.33	2.129	43	16.28[b]	2.872	51	18.34	2.098	40	20.36[b]	3.458	50
	80	19.19	2.692	41	17.15[b]	2.730	44	19.35	2.431	38	20.93[b]	2.898	49

N - Number of measures used to calculate mean
SD - Standard Deviation

[a]Significantly different from control; (p<0.05)
[b]Significantly different from control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Food Consumption Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day Mean	0 mg/kg/day SD	0 mg/kg/day N	1 mg/kg/day Mean	1 mg/kg/day SD	1 mg/kg/day N	50 mg/kg/day Mean	50 mg/kg/day SD	50 mg/kg/day N	500 mg/kg/day Mean	500 mg/kg/day SD	500 mg/kg/day N
Food Consumption g/animal/day													
	82	19.87	2.343	41	18.88	1.764	43	19.59	3.163	35	20.71	3.009	47
	84	18.29	2.846	41	18.29	3.029	42	19.12	4.496	34	20.12[a]	3.679	44
	86	17.99	3.894	40	17.24	2.427	39	19.58	2.878	31	20.24[b]	3.334	37
	88	16.91	3.836	34	18.20	2.001	35	20.67[b]	3.036	30	20.09[b]	3.378	33
	90	17.03	3.991	30	18.62	2.518	31	19.30[a]	3.342	24	20.49[b]	3.582	30
	92	16.75	4.537	26	18.77	2.532	28	19.51[a]	2.866	21	20.57[b]	3.880	25
	94	17.31	3.853	23	18.77	3.234	26	18.46	5.172	20	21.12[b]	3.863	24
	96	18.82	3.238	20	18.86	3.580	25	19.25	4.025	18	21.22	4.101	24
	98	17.58	5.115	18	17.95	3.668	23	20.01	3.380	17	21.58[b]	3.473	20
	100	19.02	4.144	17	18.32	4.131	22	19.17	4.384	17	20.51	3.222	18

N - Number of measures used to calculate mean
SD - Standard Deviation

[a]Significantly different from control; (p<0.05)
[b]Significantly different from control; (p<0.01)

Table 7
Summary of Food Efficiency Values

Study Number
DuPont-18405-1238
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Estimated Food Efficiency Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Efficiency %	1-13	13.00	1.461	79	13.07	1.677	79	13.13	1.358	80	11.87[b]	1.440	80

N - Number of measures used to calculate mean
SD - Standard Deviation

[b]Significantly different from the control; ($p<0.01$)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Estimated Food Efficiency Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Efficiency %	1-52	5.63	0.708	75	5.76	0.797	71	5.74	0.832	73	5.22[b]	0.646	77

N - Number of measures used to calculate mean
SD - Standard Deviation

[b]Significantly different from the control; ($p<0.01$)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Estimated Food Efficiency Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Efficiency %	1-102	2.79	0.752	17	3.09	0.726	20	2.59	0.671	19	2.82	0.474	18

N - Number of measures used to calculate mean
SD - Standard Deviation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Estimated Food Efficiency Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day Mean	SD	N	0.1 mg/kg/day Mean	SD	N	1 mg/kg/day Mean	SD	N	50 mg/kg/day ppm Mean	SD	N
Food Efficiency %													
	2	29.68	2.894	79	29.39	3.649	80	30.30	2.848	80	30.58[a]	4.704	80
	3	25.20	3.854	79	25.16	4.165	80	25.71	3.623	80	23.24[b]	4.165	80
	4	21.30	4.115	80	21.73	3.487	79	21.90	2.867	78	18.63[b]	3.797	80
	5	18.19	3.476	80	17.88	3.927	79	16.60[b]	3.713	80	14.54[b]	3.894	80
	6	15.75	3.637	80	15.56	3.811	79	17.22[b]	3.701	76	15.22	5.926	80
	7	11.61	2.960	80	11.10	2.756	79	10.66	2.926	80	9.15[b]	3.970	80
	8	11.39	2.857	80	12.09	3.405	79	11.61	4.134	80	10.28	3.529	80
	9	8.38	3.243	80	8.59	2.818	79	8.34	4.917	80	7.17	4.244	80
	10	8.50	3.120	80	7.35	3.412	77	8.38	3.655	80	8.27	3.218	80
	11	7.83	3.570	80	9.22[b]	3.840	79	7.66	2.629	80	7.56	2.798	80
	12	4.92	3.965	80	4.99	2.807	79	5.94	3.079	80	3.57	7.305	80
	13	6.08	4.634	80	5.60	4.152	78	5.10	4.712	80	4.66[a]	4.747	80
	14	5.44	3.712	80	6.12	3.209	78	6.91[a]	3.782	78	7.28[b]	3.873	80
	16	5.04	3.090	80	5.20	2.269	78	4.90	2.004	80	4.72	1.917	80
	18	5.54	2.307	80	5.44	2.198	78	5.49	2.071	80	4.78	1.918	80
	20	4.74	2.011	78	3.66[b]	2.318	38	4.18	1.580	80	4.15	2.041	80
	22	4.24	2.210	80	4.73	1.687	77	4.54	2.029	80	3.78	2.496	80
	24	3.45	2.311	80	3.09	2.094	77	3.50	2.267	80	2.66[a]	2.429	80
	26	4.21	2.107	78	3.36[a]	2.122	77	2.73[b]	3.518	80	2.91[b]	2.961	80
	28	3.51	2.712	79	3.23	3.061	77	4.35	3.010	78	3.05	3.340	80
	30	3.19	2.018	76	3.47	2.127	77	3.36	2.618	79	3.90	3.084	80
	32	3.95	1.897	78	2.60[b]	2.129	71	2.51[b]	2.374	77	3.34	2.745	78
	34	2.39	1.814	78	4.10[b]	2.211	77	3.86[b]	2.556	77	3.11[a]	2.202	80
	36	2.77	2.187	78	1.33[b]	2.948	77	1.10[b]	2.774	78	1.84	2.332	80
	38	2.93	3.232	78	2.55	2.687	76	4.00[b]	2.668	77	2.49	2.378	80
	40	2.25	2.150	78	2.57	2.209	74	1.68	2.978	77	2.53	2.371	80
	42	2.44	2.200	74	3.10	2.329	76	0.96	4.918	77	1.07[a]	4.035	80
	44	1.32	2.040	77	1.40	2.004	75	1.34	5.877	73	2.13	2.313	80
	46	1.53	2.174	76	1.02	2.895	75	2.84[b]	2.599	73	1.84	2.243	80
	48	0.60	3.474	76	2.65[b]	2.837	73	1.29	4.130	74	1.48	2.428	79

N - Number of measures used to calculate mean
SD - Standard Deviation

[a]Significantly different from the control; (p<0.05)
[b]Significantly different from the control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Estimated Food Efficiency Values - MALE

Endpoint	Study Interval (Week)	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day ppm		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Efficiency %													
	50	3.55	3.653	76	1.91[a]	5.888	72	2.15[b]	2.691	74	1.25[b]	8.341	79
	52	0.09	5.128	76	1.23	2.717	69	1.14	3.526	72	1.34	4.267	75
	54	-2.11	7.434	66	1.52[b]	2.640	61	0.65[b]	4.132	62	0.15[b]	5.246	67
	56	3.15	2.672	64	3.35	2.751	60	1.64[a]	3.119	62	2.22	4.177	65
	58	1.08	4.820	64	1.37	3.829	59	2.85[b]	4.796	60	1.52	2.917	62
	60	1.22	7.309	63	0.22[a]	5.354	55	-0.72[b]	7.791	58	2.11	3.394	59
	62	-0.67	12.082	63	1.14	2.687	57	-1.00[b]	4.347	56	-1.21	6.898	57
	64	1.61	4.067	61	1.82	2.826	56	2.34	3.432	56	1.83	3.032	53
	66	-0.52	5.257	59	1.30[a]	2.774	54	0.04	4.067	54	-0.25	7.579	52
	68	-0.48	6.413	58	-0.95	4.735	55	-2.69[a]	13.236	52	1.03	2.720	51
	70	-0.21	4.240	55	1.77[b]	5.205	55	2.07[b]	3.791	48	1.81[b]	3.852	51
	72	2.37	3.877	53	-1.04[b]	12.963	53	1.96	2.921	47	0.34[b]	4.767	50
	74	0.67	4.714	51	0.85	3.549	52	-2.34[a]	10.012	46	1.41	3.536	49
	76	-4.38	23.075	52	0.35	6.555	51	0.51[a]	8.563	45	2.09[b]	4.121	47
	78	-2.74	16.031	51	-0.93	4.881	50	-2.87	7.911	42	-2.04	9.444	49
	80	-0.94	5.484	48	-0.91	4.246	49	-1.32	8.055	36	-2.37	10.128	46
	82	-0.16	7.287	47	-1.32	5.478	48	-0.55	3.915	34	-1.58	11.617	42
	84	-2.69	9.728	46	-2.94	11.861	47	-6.41	43.776	34	-2.58	15.111	41
	86	-5.44	33.670	43	0.46	4.864	43	-0.37	6.172	33	-1.48	8.315	38
	88	-2.31	8.376	40	-0.48	3.076	43	-6.78	13.781	31	-1.88	6.198	35
	90	-4.17	16.886	36	-0.00	9.724	40	-23.51	113.719	28	0.39	2.497	32
	92	-10.68	49.649	31	-5.54	18.620	36	-5.57	20.087	25	-0.94	5.794	29
	94	-4.02	9.103	30	-2.45	9.616	30	-4.55	11.547	26	-0.05	4.238	27
	96	-3.67	7.891	27	-5.09	10.214	28	-2.65	4.752	24	0.94[a]	3.801	27
	98	-7.46	11.433	25	-1.88[a]	9.574	27	-3.73	7.493	22	0.54[b]	6.836	26
	100	-5.28	7.806	19	-7.61	10.507	24	-7.45	13.339	21	-1.29	9.027	26
	102	-2.97	6.927	18	-5.01	10.149	20	-6.79	15.953	20	-4.35	10.215	23

N - Number of measures used to calculate mean
SD - Standard Deviation

[a]Significantly different from the control; ($p<0.05$)
[b]Significantly different from the control; ($p<0.01$)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Estimated Food Efficiency Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Efficiency %	1-13	7.54	1.212	80	7.21	1.133	80	7.76	1.106	80	7.37	0.921	80

N - Number of measures used to calculate mean
SD - Standard Deviation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Estimated Food Efficiency Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Efficiency %	1-52	4.21	0.840	74	3.93	0.690	77	4.29	0.812	73	3.26[b]	0.682	75

N - Number of measures used to calculate mean
SD - Standard Deviation

[b]Significantly different from the control; ($p<0.01$)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Estimated Food Efficiency Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Efficiency %	1-100	2.42	0.431	17	2.58	0.605	22	2.74	0.485	17	2.15	0.412	19

N - Number of measures used to calculate mean
SD - Standard Deviation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Estimated Food Efficiency Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day Mean	SD	N	1 mg/kg/day Mean	SD	N	50 mg/kg/day ppm Mean	SD	N	500 mg/kg/day Mean	SD	N
Food Efficiency %													
	2	16.83	4.467	80	16.73	3.894	80	18.01	4.264	80	18.66[a]	3.329	80
	3	15.20	4.675	80	16.07	4.201	80	16.27	4.178	80	16.48	3.721	80
	4	13.92	4.466	78	12.07	7.894	78	13.66	4.465	80	12.52[a]	3.719	80
	5	9.77	3.890	76	7.07[a]	9.967	80	7.90[a]	4.498	80	9.52	3.172	80
	6	9.41	3.643	80	11.07	6.069	80	10.76	3.940	80	11.09[a]	4.311	80
	7	4.05	4.668	80	4.01	5.189	80	4.84	4.084	80	4.39	3.856	80
	8	7.20	3.803	80	7.26	3.908	80	6.70	4.577	80	5.53[b]	3.488	80
	9	3.68	4.236	80	5.40[a]	4.174	80	4.25	3.263	80	5.28	3.934	80
	10	2.64	4.575	80	2.77	4.361	80	3.62	4.335	80	3.20	3.457	80
	11	6.97	8.737	80	4.75	4.302	80	5.48	4.446	80	3.80[b]	3.445	80
	12	4.21	3.951	80	4.06	3.825	80	4.35	6.419	80	3.00	3.601	80
	13	3.68	6.183	80	1.43[b]	4.548	80	4.26	6.494	80	1.88[b]	4.025	80
	14	3.82	4.985	80	6.30[b]	4.877	80	2.78	5.343	80	5.69[a]	4.562	80
	16	3.02	3.092	80	2.76	2.397	80	3.07	2.845	80	0.87[b]	2.935	80
	18	3.20	2.866	80	3.42	2.387	80	4.14	2.607	80	3.98	2.089	80
	20	2.37	4.118	80	2.70	2.753	80	4.22[b]	2.626	80	3.16	2.240	80
	22	3.44	2.708	80	3.48	2.973	80	2.86	3.402	80	1.93[b]	2.660	80
	24	2.02	3.198	80	0.57	4.383	78	2.68	2.512	80	0.75[a]	2.760	80
	26	3.41	3.050	78	3.08	3.165	80	3.24	2.488	79	2.52[a]	2.449	80
	28	3.47	3.015	80	3.42	3.623	78	2.42	3.268	79	0.49[b]	3.544	80
	30	3.09	2.925	80	3.17	3.338	80	3.00	3.047	79	2.11	2.638	79
	32	4.67	3.442	80	3.35[b]	2.575	79	5.08	2.548	79	2.33[b]	2.800	79
	34	2.51	2.712	80	3.22	2.697	79	2.64	2.427	79	2.84	2.728	79
	36	2.50	3.650	80	1.06	4.979	79	2.08	2.707	79	-0.03[b]	2.683	79
	38	4.23	3.721	78	3.51	4.931	79	4.53	2.981	78	1.67[b]	2.547	79
	40	3.71	2.730	79	2.41[a]	2.703	78	1.22[b]	2.544	78	1.69[b]	2.134	79
	42	1.78	3.036	79	1.44	4.475	76	2.96[a]	2.584	77	1.23	4.866	79
	44	1.32	3.048	79	3.24[b]	3.074	77	1.66	4.354	77	2.43	4.020	79
	46	1.99	3.583	78	2.64	3.152	77	2.47	4.580	76	0.73[b]	2.785	76
	48	4.46	3.654	78	1.75[b]	2.938	77	2.63[a]	3.148	74	0.61[b]	3.422	78

N - Number of measures used to calculate mean
SD - Standard Deviation

[a]Significantly different from the control; (p<0.05)
[b]Significantly different from the control; (p<0.01)

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Estimated Food Efficiency Values - FEMALE

Endpoint	Study Interval (Week)	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day ppm			500 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Efficiency %													
	50	3.44	7.742	75	3.20	3.560	77	3.32	4.234	74	2.85[a]	3.492	78
	52	2.91	4.457	74	1.50	4.401	77	3.18[a]	8.014	70	1.03[b]	3.842	75
	54	-1.83	4.903	63	-0.57	5.007	66	-4.19	16.512	62	0.62[b]	4.999	65
	56	5.35	3.700	62	2.63[a]	6.557	65	3.72	4.437	60	2.44[b]	4.617	65
	58	2.99	4.076	61	3.74	3.848	64	3.63	2.808	58	0.92[b]	3.299	61
	60	2.19	5.713	59	1.84	7.017	63	0.01	11.467	58	-1.16[b]	4.199	59
	62	-1.13	5.048	58	-1.09	3.754	62	-2.86	14.206	55	1.48[b]	2.888	59
	64	-0.56	11.449	58	3.20	3.354	59	2.91[a]	7.079	53	2.78	3.917	59
	66	-0.88	10.889	56	1.29	3.735	59	1.01	7.231	53	0.77	5.447	59
	68	-3.13	22.661	51	0.77	3.676	59	1.40	4.894	51	-2.02[a]	5.001	58
	70	1.90	3.447	48	0.91	13.005	58	2.06	5.935	49	4.22[b]	3.251	56
	72	3.23	3.888	47	2.05	5.949	58	-0.72[b]	8.259	49	-0.94[b]	4.040	56
	74	0.87	8.589	44	-1.11	8.223	56	0.50	8.779	49	3.27	4.477	54
	76	2.04	6.489	42	-4.28[b]	12.664	53	0.44	5.399	44	0.41	8.115	52
	78	-3.63	5.135	43	-6.25	11.743	51	-0.08[b]	4.359	40	-1.04[a]	5.670	50
	80	-3.20	4.057	41	-3.42	7.387	44	-2.28	6.718	38	-1.43[b]	6.064	49
	82	2.64	3.248	41	1.09	5.018	43	-0.87[a]	8.043	35	-0.80[b]	3.951	47
	84	-1.90	6.617	41	0.20	9.521	42	-6.82[b]	46.873	34	1.42[b]	8.761	44
	86	-1.91	12.330	40	-2.66	9.199	39	1.69	5.979	31	1.19	3.465	37
	88	-5.54	11.418	34	0.50[a]	4.988	35	0.97[a]	5.987	30	-1.21	3.517	33
	90	-6.87	17.766	30	0.92	3.386	31	-0.36	6.611	24	2.34[b]	4.284	30
	92	-5.73	20.254	26	0.83	4.222	28	-0.26	5.610	21	-0.72	6.082	25
	94	-3.33	14.390	23	-1.07	13.180	26	-25.37	100.457	20	1.72	4.780	24
	96	-2.88	8.117	20	0.27	7.183	25	-2.24	13.244	18	2.63[b]	4.550	24
	98	-5.81	21.796	18	-0.67	5.578	23	-0.57	8.100	17	0.56	3.302	20
	100	-4.34	13.076	17	-3.95	13.652	22	-0.80	8.748	17	0.30	2.853	18

N - Number of measures used to calculate mean
SD - Standard Deviation

[a]Significantly different from the control; ($p<0.05$)
[b]Significantly different from the control; ($p<0.01$)

Table 8
Summary of Ophthalmoscopic Examination Findings

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Ophthalmoscopic Examination Findings - MALE

Pretest

	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number Examined	80	80	80	80
Number With No Abnormalities Detected	80	80	80	80
Cataract - Cortical axial posterior	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0
Cataract - Mature	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0
Chorioretinal hypoplasia	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0
Conjunctivitis	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0
Keratitis - Superficial	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0
Microphthalmia	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0

( ) - Number of animals with observation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Ophthalmoscopic Examination Findings - MALE

Pretest

	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Retinal atrophy	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0

( ) - Number of animals with observation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Ophthalmoscopic Examination Findings - MALE

Interim

	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number Examined	76	71	73	77
Number With No Abnormalities Detected	76	67	71	76
Cataract - Cortical axial posterior	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0
Cataract - Mature	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0
Chorioretinal hypoplasia	(0)	(1)	(2)	(1)
Right Eye	0	0	2	1
Left Eye	0	1	0	0
Conjunctivitis	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0
Keratitis - Superficial	(0)	(2)	(0)	(0)
Right Eye	0	1	0	0
Left Eye	0	2	0	0
Microphthalmia	(0)	(1)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	1	0	0

( ) - Number of animals with observation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Ophthalmoscopic Examination Findings - MALE

Interim

	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Retinal atrophy	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0

( ) - Number of animals with observation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Ophthalmoscopic Examination Findings - MALE

Terminal

	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number Examined	18	20	20	23
Number With No Abnormalities Detected	11	18	15	17
Cataract - Cortical axial posterior	(1)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	1	0	0	0
Cataract - Mature	(2)	(0)	(0)	(1)
Right Eye	2	0	0	1
Left Eye	1	0	0	1
Chorioretinal hypoplasia	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0
Conjunctivitis	(1)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	1	0	0	0
Keratitis - Superficial	(4)	(1)	(5)	(5)
Right Eye	2	1	5	4
Left Eye	4	1	5	5
Microphthalmia	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0

( ) - Number of animals with observation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Ophthalmoscopic Examination Findings - MALE

Terminal

	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Retinal atrophy	(0)	(1)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	1	0	0

( ) - Number of animals with observation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Ophthalmoscopic Examination Findings - FEMALE

Pretest

	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number Examined	80	80	80	80
Number With No Abnormalities Detected	80	80	80	80
Chorioretinal hypoplasia	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0
Conjunctivitis	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0

( ) - Number of animals with observation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Ophthalmoscopic Examination Findings - FEMALE

Interim

	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number Examined	74	77	72	75
Number With No Abnormalities Detected	71	75	70	74
Chorioretinal hypoplasia	(2)	(1)	(2)	(1)
Right Eye	2	0	2	1
Left Eye	0	1	0	0
Conjunctivitis	(1)	(1)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	1	1	0	0

( ) - Number of animals with observation

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Ophthalmoscopic Examination Findings - FEMALE

Terminal

	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number Examined	8	11	7	9
Number With No Abnormalities Detected	7	10	7	9
Chorioretinal hypoplasia	(0)	(0)	(0)	(0)
Right Eye	0	0	0	0
Left Eye	0	0	0	0
Conjunctivitis	(1)	(1)	(0)	(0)
Right Eye	1	1	0	0
Left Eye	0	1	0	0

( ) - Number of animals with observation

Appendix A
Vehicle and Test Article Information

Vehicle and Test Article Information

Date Received:	July 14, 2010
Supplier:	
Amount Received:	Approximately 30,000 g in three containers
Label Identification:	also referred to as
Lot Number:	
Physical Characteristics:	Clear, colorless liquied
Expiration Date:	June 13, 2015
Storage:	Room temperature
Number:	

Deionized water was provided by

CERTIFICATE OF ANALYSIS

This Certificate of Analysis fulfills the requirement for characterization of a test substance prior to a study subject to GLP regulations. It documents the identity and content of the test substance. Portions of this work were not conducted under EPA Good Laboratory Practice Standards (40 CFR 792).

Code Number	
Common Name	
Purity Percent	84%
Other Components	
Date of Analysis	June 13, 2008
Expiration Date	June 13, 2015
Instructions for storage	NRT&H
Reference	
Analysis performed at	

31-MAY-2011
Date

Revision #1: Revised COA expiration date based on compound stability assessment. 6/23/09
Revision #2: Revised COA expiration date based on compound stability assessment. 3/8/11

Appendix B
Formulation Analysis Report

COMBINED CHRONIC TOXICITY/ONCOGENICITY STUDY
2-YEAR ORAL GAVAGE STUDY IN RATS

FORMULATION ANALYSIS REPORT

TEST ARTICLE:

TEST SITE:

STUDY NUMBER:

PRINCIPAL INVESTIGATOR:

TESTING FACILITY:

STUDY DIRECTOR:

SPONSOR:

LABORATORY PROJECT ID:

GOOD LABORATORY PRACTICE COMPLIANCE STATMENT

The work conducted and reported in the analytical report of this nonclinical laboratory study was conducted in accordance with the United States Environmental Protection Agency (EPA) Toxic Substance Control Act (TSCA) Good Laboratory Practice (GLP) Standards, 40 CFR Part 792, the Organization for Economic Cooperation and Development (OECD) Principles of GLP ENV/MC/CHEM(98)17, and the Japanese GLP Standards, 11 Nohsan Number 6283 and as changed in Nohsan Number 8628, and 13 Seisan Number 1660. No exceptions from these regulations occurred during the course of the study. No protocol deviations occurred during the course of this study. This report accurately reflects the raw data obtained during the performance of this study phase.

27 Mar 2013
Date

Date

Typed name of signer: .....

QUALITY ASSURANCE STATEMENT

Below are the inspections conducted by the and the dates the inspections were reported to the Principal Investigator and Management and to the Study Director and Management for l

Date(s) of Inspection	Study Phase Inspected	Date(s) Reported to Principal Investigator	Date(s) Reported to Study Director and Testing Site and Test Facility Management
9/23/10 and 9/28/10	Protocol, Protocol Amendment1 and Standard Solution Preparation	9/28/10	9/28/10
2/28/11 and 3/1/11	Protocol Amendments 2 and 3 and Standard Solution Preparation	3/1/11	3/1/11
11/30/11 and 12/13/11	Protocol Amendment 4 and Instrument Set-Up	12/13/11	12/13/11
7/6/12 and 7/9/12	Protocol Amendment 5, Raw Data, Summary Tables and Draft Report	7/10/12	7/10/12
3/25/13	Final Report	3/25/13	3/25/13
3/25/13	Protocol Amendments 6, 7 and 8	3/26/13	3/26/13

The Quality Assurance Department has confirmed that the methods, procedures, and observations are accurately and completely described, and that the reported results accurately reflect the raw data.

3/27/13
Date

CERTIFICATION

We, the undersigned, declare that this report provides an accurate evaluation of data obtained from this study phase.

27Mar2013
Date

27 March 2013
Date

TABLE OF CONTENTS

TABLE OF CONTENTS

1. KEY PERSONNEL

2. INTRODUCTION

This study phase was conducted for for analysis of the test article, in dosing formulation samples. This study phase was conducted in accordance with Standard Operating Procedures (SOPs) and the protocol as approved by the Sponsor. Two SOP deviations were acknowledged by the Study Director, documented in the raw data, and are presented in Section 6. In the opinion of the Study Director, the SOP deviations were considered not to have affected the quality or integrity of the study. The analytical method is presented in Appendix B. The computer systems used during the conduct of this study phase are presented in Appendix C. Procedures pertinent to this study phase are described in this report.

2.1. Study Phase Schedule

Protocol Approved by Sponsor	July 12, 2010
Study Initiation Date (Protocol Signed by Study Director)	July 12, 2010
Experimental Starting Date (Date of Receipt of First Samples)	August 5, 2010
Experimental Start Date (Date of First Sample Dilution)	August 7, 2010
Experimental Termination Date (Date of Last Sample Injection)	May 23, 2012
Experimental Completion Date (Date of Last Sample Injection)	May 23, 2012
Draft Report Mail Date	July 16, 2012

2.2. Analytical History

The following table describes the injection dates and objectives for the analytical runs evaluated during the course of the study phase to determine the homogeneity and concentration of in dosing formulation samples from Study Number

Analytical Run History

Run	Sample Processing Date	Run Date	Run Objective	Method Version Used	Data Used for Reporting
080710A	8/7/10	8/7/10	SA (Week 1 H and C)	125-128-A-01	Yes
081410A	8/14/10	8/14/10	SA (Week 2 C)	125-128-A-01	Yes
082110A	8/21/10	8/21/10	SA (Week 3 C)	125-128-A-01	Yes
082710A	8/27/10	8/27/10	SA (Week 4 C)	125-128-A-01	Yes
112910A	11/29/10	11/29/10	SA (Week 17 C)	125-128-A-01	Yes
022811A	2/28/11	2/28/11	SA (Week 30 C)	125-128-A-01	Yes
030111A	3/1/11	3/1/11	Backup SA (Week 30 C)	125-128-A-01	Yes
060611A	6/6/11	6/6/11	SA (Week 44 C)	125-128-A-01	Yes
060711A	6/7/11	6/7/11	Backup SA (Week 44 C)	125-128-A-01	Yes
061611A	6/16/11	6/16/11	SA (Week 47 C)	125-128-A-01	No[a]
061711A	6/17/11	6/17/11	Backup SA (Week 47 C)	125-128-A-01	No[a]
062611A	6/26/11	6/26/11	Backup SA (Week 47 C)	125-128-A-01	Yes
062611B	6/26/11	6/26/11	SA (Week 48 C)	125-128-A-01	Yes
063011A	6/30/11	6/30/11	Backup SA (Week 48 C)	125-128-A-01	Yes
082611A	8/26/11	8/26/11	SA (Week 56 C)	125-128-A-01	Yes
083011A	8/30/11	8/30/11	Backup SA (Week 56 C)	125-128-A-01	Yes
113011A	11/30/11	11/30/11	SA (Week 69 C)	125-128-A-01	Yes
022712A	2/27/12	2/27/12	SA (Week 82 C)	125-128-A-01	Yes
022812A	2/28/12	2/28/12	Backup SA (Week 82 C)	125-128-A-01	Yes
052212	5/22/12	NA	SA (Week 95 C)	125-128-A-01	No[b]
052212A[c]	5/22/12	5/23/12	SR (Week 95 C)	125-128-A-01	Yes

C – Concentration
H – Homogeneity
NA – Not Applicable/Not Available
SA – Sample Analysis
SR – Sample Reanalysis

[a]Calibration curve and two performance check standards failed to meet acceptance criteria.
[b]Incorrect vial positions for several samples.
[c]Reinjection of analytical run 052212.

Data not used for reporting are maintained in the study file. Some preparation data from these runs were used for reported analytical runs and are presented in this report, as applicable.

3. MATERIALS AND METHODS

3.1. Reference Standard Information

The test article was used as the reference standard. Pertinent reference standard information is presented in Appendix A.

The Sponsor has provided documentation of the purity, composition, stability, and other pertinent information for the lot of the reference standard, used on study.

3.2. Reserve Sample

The test article was used as the reference standard. A reserve sample from the lot of reference standard was not retained by the site performing sample analysis.

3.3. Formulation Analysis

A detailed summary of the experimental conditions, including materials, methods, and sample processing procedures is included in the analytical method.

3.3.1. Sample Receipt

A total of 480 dosing formulation samples were received from in 13 shipments on August 5, 2010, August 12, 2010, August 19, 2010, August 26, 2010, November 23, 2010, February 23, 2011, June 2, 2011, June 16, 2011, June 23, 2011, August 25, 2011, November 22, 2011, February 21, 2012, and May 22, 2012. Samples were received frozen on dry ice and stored in a freezer set to -20°C. Documentation of sample storage following analysis is maintained in the study file.

3.3.2. Sample Analysis

Dosing formulation samples were processed and analyzed according to the procedures outlined in the analytical method validated under

3.3.3. Formulation Sample Acceptance Criteria

The acceptance criteria for the homogeneity and concentration samples were an average concentration within ±10% recovery of the nominal concentration and a relative standard deviation (RSD) ≤5% from the start of sample analysis through June 28, 2011. The acceptance criteria for the concentration samples were an average concentration within ±10% recovery of the nominal concentration and a relative standard deviation (RSD) ≤10% from June 29, 2011 through the end of the study due to a change in the standard operating procedure (SOP) for dose formulation sample analysis. The response of the test article in vehicle samples was required to have been less than or equal to the lower limit of quantitation (LLOQ, 0.5 ng/mL).

3.4. Data Retention

All raw data, documentation, records, protocol, samples, and the final report generated as a result of this study phase will be retained at , or an approved archive facility contracted by for a period of 1 year following issuance of the draft report. The Sponsor will be contacted annually by Archive staff regarding the retained

material and will be responsible for the incurred costs for the return, disposal, or continued storage of any study generated material retained after that time.

4. RESULTS AND DISCUSSION

4.1. System Performance

4.1.1. System Suitability Test

A summary of the system suitability test (SST) parameters is presented in Table 1. Replicate injections of an independent preparation were used to determine system suitability for each run. The acceptance criteria for SST were as follows: injection repeatability (peak area relative standard deviation [RSD]) ≤10% and signal to noise ratio ≥100. The peak area RSD was consistently ≤6.798% for all passing runs. The signal to noise ratio was consistently ≥161.1 for all passing runs. The SST parameters met the acceptance criteria for all passing runs.

4.1.2. Performance Check Standards

A summary of the performance check standard results is presented in Table 2. Injections of the performance check standard (same solution as the SST standards) were performed periodically throughout the runs. The acceptance criterion for the performance check standards was 100 ±10% recovery of the nominal concentration. Samples are considered valid if they are bracketed by two performance check standards that meet the acceptance criterion.

4.1.3. Calibration Curve

A summary of the calibration curve results is presented in Table 3. A multi-point calibration curve was used for quantification by injecting six standards. The acceptance criterion for the calibration curve was a coefficient of determination (R^2) ≥0.990 and the acceptance criterion for the individual standards was a concentration of 100 ±10% recovery of the nominal concentration. At least 5 of the 6 calibration standards must be within 100 ±10% recovery of the nominal concentration. All of the passing runs met the acceptance criteria for accuracy and linearity.

4.2. Analysis of Dosing Formulations

4.2.1. Homogeneity

A summary of the homogeneity analysis of in dosing formulations is presented in Table 4. Week 1 dose formulations were analyzed for homogeneity verification. Two samples from the top, middle, and bottom of the 0.01 mg/mL, 0.1 mg/mL, 5.0 mg/mL, and 50 mg/mL concentration were injected and analyzed. Samples for each level met the sample analysis acceptance criteria for accuracy and precision (100 ±10% average recovery, ≤5% RSD).

4.2.2. Concentration

A summary of the concentration analysis of in dosing formulations is presented in Table 5. Weeks 1, 2, 3, 4, 17, 30, 44, 47, 48, 56, 69, 82, and 95 dose formulations were analyzed for concentration verification. Duplicate samples from the middle stratum at the 0.0 mg/mL (vehicle control), 0.01 mg/mL, 0.1 mg/mL, 5.0 mg/mL, and 50 mg/mL concentration were injected and analyzed. Duplicate samples from the top, middle, bottom stratum at the 0.01 mg/mL concentration from the Week 44 dosing formulations were also injected and analyzed. Samples for each level met the sample analysis acceptance criteria for accuracy and precision (100 ±10% average recovery, ≤5% RSD through June 28, 2011 and 100 ±10% average

recovery, ≤10% RSD from June 29, 2011 through the end of the study), with the following exceptions.

- Week 30 samples at the 5.0 mg/mL concentration failed to meet the acceptance criterion for recovery, and Week 30 samples at the 50 mg/mL concentration failed to meet the acceptance criteria for both recovery and RSD. The backup samples were analyzed. The Week 30 backup samples met acceptance criteria but when averaged with original results the 50 mg/mL concentration still failed to meet acceptance criteria for recovery.
- Week 44 samples at the 0.01 mg/mL, 0.1 mg/mL, 5.0 mg/mL, and 50 mg/mL concentrations failed to meet acceptance criteria for recovery, and backup samples were analyzed. The Week 44 backup samples confirmed the original results and still failed to meet acceptance criteria for recovery. Based on these unacceptable results, protocol amendment 5 was issued to require analysis of the Week 47 and Week 48 samples. The results for the Week 44 samples at the 0.1 mg/mL, 5.0 mg/mL, and 50 mg/mL concentrations were outside the acceptability criteria range (100 ±10% average recovery), but the average % recovery ranged from 81.1-82.9% of nominal.
- The results for the 0.01 mg/mL concentration samples were approximately double the nominal concentration. This indicates that animals dosed with this formulation (males only) received approximately double the intended dose over that week.
- The original analysis and backup analysis of the Week 47 samples at all concentrations were not reported due to the calibration curve and performance check standards failing to meet to acceptance criteria. A second set of Week 47 backup samples were analyzed for all concentrations and the 0.1 mg/mL and 5.0 mg/mL concentrations failed to meet the acceptance criterion for recovery.
- Week 48 samples at the 0.01 mg/mL concentration had an unaccepted RSD result, and backup samples were analyzed. The Week 48 backup sample results were within ±10.0% difference of the original results and were averaged with the original results. The averaged results failed to meet the acceptance criterion for recovery.
- Week 56 samples at the 0.01 mg/mL and 0.1 mg/mL concentrations failed to meet acceptance criteria for recovery, and backup samples were analyzed. The Week 56 backup samples confirmed the original results and still failed to meet acceptance criteria for recovery.
- Week 82 samples at the 0.01 mg/mL, 0.1 mg/mL, 5.0 mg/mL, and 50 mg/mL concentrations failed to meet the acceptance criterion for recovery, ranging from 78.7% to 88.3%. In addition, the 0.1 mg/mL, 5.0 mg/mL, and 50 mg/mL concentrations were not bracketed by acceptable performance check standards. As a result, the backup samples were analyzed. The Week 82 backup samples at the 0.01 mg/mL, 5.0 mg/mL, and 50 mg/mL concentrations confirmed the original results. When averaged together with the original results, the 5.0 mg/mL concentration met all acceptance criteria, but the 0.01 mg/mL and 50 mg/mL concentrations failed to meet acceptance criteria for recovery. The Week 82 backup samples at the 0.1 mg/mL concentration did not confirm the original results and were reported separately. The backup sample results at this concentration failed to meet the acceptance criterion for RSD.

5. CONCLUSION

All SST, performance check, and calibration standards met the sample analysis acceptance criteria. Dose formulation samples were analyzed for homogeneity and concentration verification. Test article was not detected in the vehicle control samples. All samples met the sample analysis acceptance criteria for accuracy and precision (average concentration within ±10% recovery of the nominal concentration, ≤5% RSD through June 28, 2011, ≤10% RSD from June 29, 2011 through the end of the study), with a few exceptions. The concentration of the 0.01 mg/mL formulation was demonstrated to be approximately double the nominal concentration during week 44. This indicates that animals dosed with this formulation (males only) received approximately double the intended dose over that week.

6. DEVIATIONS

This study was conducted in accordance with the SOPs except for the following deviations.

In run 052212A, a Week 95 0.1 mg/mL concentration sample did not elute within 10% of the reference standard retention time. Both samples at this concentration met acceptance criteria for overall recovery and RSD.

In run 060611A, the times samples were transferred from the freezer, aliquoted, and transferred back to the freezer were not recorded on one of the secondary sample solutions prep sheets. The times samples were transferred from and to Freezer 36 were documented in Exylims and were transcribed in the data as 7:32 am and 11:05 am, respectively. The exact time when samples were aliquoted is not known, but would have been between to the transfers from and to frozen storage.

Protocol amendments 6, 7, and 8 inadvertently underwent an additional review by Quality Assurance at the test site in .

In the opinion of the Study Director, these deviations did not affect the quality or integrity of the study.

Tables

Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Table 1 **System Suitability Test Parameters**

Analytical Run	Standard Identification	Peak Area	Signal to Noise Ratio
080710A	SST Injection 1	982620	428.4
	SST Injection 2	975566	382.9
	SST Injection 3	968344	501.4
	Mean	975510	438
	%RSD	0.732	13.7
081410A	SST Injection 1	950451	446.8
	SST Injection 2	953315	360.6
	SST Injection 3	951677	343.5
	Mean	951814	384
	%RSD	0.151	14.4
082110A	SST Injection 1	939996	206.5
	SST Injection 2	946721	244.1
	SST Injection 3	951537	300.6
	Mean	946085	250.4
	%RSD	0.613	18.9
082710A	SST Injection 1	953499	387.1
	SST Injection 2	943471	314.4
	SST Injection 3	934008	362.5
	Mean	943659	354.7
	%RSD	1.033	10.4

RSD -Relative Standard Deviation
SST -System Suitability Test

Table 1 **System Suitability Test Parameters**

Analytical Run	Standard Identification	Peak Area	Signal to Noise Ratio
112910A	SST Injection 1	875281	381.8
	SST Injection 2	883600	360.8
	SST Injection 3	893288	373.3
	Mean	884056	372.0
	%RSD	1.019	2.8
022811A	SST Injection 1	366981	487.3
	SST Injection 2	356081	399.8
	SST Injection 3	356961	504.8
	Mean	360008	464.0
	%RSD	1.682	12.1
030111A	SST Injection 1	346235	486.2
	SST Injection 2	357891	437.6
	SST Injection 3	332368	420.1
	Mean	345498	448.0
	%RSD	3.698	7.6
060611A	SST Injection 1	352999	410.5
	SST Injection 2	347510	380.7
	SST Injection 3	353694	433.3
	Mean	351401	408.2
	%RSD	0.964	6.5

RSD -Relative Standard Deviation
SST -System Suitability Test

Table 1 **System Suitability Test Parameters**

Analytical Run	Standard Identification	Peak Area	Signal to Noise Ratio
060711A	SST Injection 1	474681	593.1
	SST Injection 2	459994	568.0
	SST Injection 3	470805	586.6
	Mean	468493	582.6
	%RSD	1.625	2.2
062611A	SST Injection 1	140574	274.4
	SST Injection 2	138842	259.2
	SST Injection 3	142246	183.4
	Mean	140554	239.0
	%RSD	1.21	20.4
062611B	SST Injection 1	141880	231.6
	SST Injection 2	151082	300.2
	SST Injection 3	146153	365.5
	Mean	146372	299.1
	%RSD	3.146	22.4
063011A	SST Injection 1	231520	163.0
	SST Injection 2	239519	165.6
	SST Injection 3	242821	154.6
	Mean	237953	161.1
	%RSD	2.442	3.57

RSD -Relative Standard Deviation
SST -System Suitability Test

Table 1 **System Suitability Test Parameters**

Analytical Run	Standard Identification	Peak Area	Signal to Noise Ratio
082611A	SST Injection 1	147508	278.8
	SST Injection 2	139403	322.9
	SST Injection 3	151694	290.7
	Mean	146202	297.5
	%RSD	4.27	7.67
083011A	SST Injection 1	141811	433.7
	SST Injection 2	144560	381.0
	SST Injection 3	140047	310.7
	Mean	142139	375.1
	%RSD	1.60	16
113011A	SST Injection 1	252367	609.5
	SST Injection 2	253789	467.6
	SST Injection 3	231257	479.7
	Mean	245804	518.9
	%RSD	5.13	15.2
022712A	SST Injection 1	103839	387.5
	SST Injection 2	101903	345.6
	SST Injection 3	102337	377.3
	Mean	102693	370.1
	%RSD	0.989	5.90

RSD -Relative Standard Deviation
SST -System Suitability Test

Table 1 **System Suitability Test Parameters**

Analytical Run	Standard Identification	Peak Area	Signal to Noise Ratio
022812A	SST Injection 1	307360	531.3
	SST Injection 2	283471	400.3
	SST Injection 3	268764	374.2
	Mean	286532	435.3
	%RSD	6.798	19.3
052212A	SST Injection 1	1600089	2056.8
	SST Injection 2	1591558	1924.5
	SST Injection 3	1596778	1864.9
	Mean	1596142	1948.7
	%RSD	0.269	5.04

RSD -Relative Standard Deviation
SST -System Suitability Test

Table 2 **Performance Check Standard Results**

Analytical Run	Standard Identification	Nominal Concentration (ng/mL)	Calculated Concentration (ng/mL)	%Recovery
080710A	Performance Check 1	5	4.857	97.1
	Performance Check 2		4.823	96.5
	Performance Check 3		4.780	95.6
	Performance Check 4		4.828	96.6
	Performance Check 5		4.747	94.9
081410A	Performance Check 1	5	4.869	97.4
	Performance Check 2		4.775	95.5
	Performance Check 3		4.788	95.8
082110A	Performance Check 1	5	4.917	98.3
	Performance Check 2		4.905	98.1
	Performance Check 3		4.872	97.4
082710A	Performance Check 1	5	4.917	98.3
	Performance Check 2		4.922	98.4
	Performance Check 3		4.864	97.3
112910A	Performance Check 1	5	5.189	104
	Performance Check 2		4.988	99.8
	Performance Check 3		5.115	102
022811A	Performance Check 1	5	4.872	97.4
	Performance Check 2		5.237	105
	Performance Check 3		4.523	90.5
030111A	Performance Check 1	5	4.880	97.6
	Performance Check 2		5.218	104

Table 2 **Performance Check Standard Results**

Analytical Run	Standard Identification	Nominal Concentration (ng/mL)	Calculated Concentration (ng/mL)	%Recovery
060611A	Performance Check 1	5	4.834	96.7
	Performance Check 2		4.427	88.5[a]
	Performance Check 3		4.749	95.0
	Performance Check 4		4.793	95.9
060711A	Performance Check 1	5	4.749	95.0
	Performance Check 2		4.660	93.2
	Performance Check 3		4.649	93.0
	Performance Check 4		4.601	92.0
062611A	Performance Check 1	5	4.798	96.0
	Performance Check 2		5.184	104
	Performance Check 3		4.892	97.8
062611B	Performance Check 1	5	4.874	97.5
	Performance Check 2		5.067	101
	Performance Check 3		4.963	99.3
063011A	Performance Check 1	5	5.262	105
	Performance Check 2		4.576	91.5
082611A	Performance Check 1	5	4.813	96.3
	Performance Check 2		4.923	98.5
	Performance Check 3		5.058	101
083011A	Performance Check 1	5	4.632	92.6
	Performance Check 2		4.585	91.7
113011A	Performance Check 1	5	4.963	99.3
	Performance Check 2		5.127	103
	Performance Check 3		5.288	106

[a] This data point failed to meet acceptance criterion for recovery (±10%).

Table 2 **Performance Check Standard Results**

Analytical Run	Standard Identification	Nominal Concentration (ng/mL)	Calculated Concentration (ng/mL)	%Recovery
022712A	Performance Check 1	5	4.708	94.2
	Performance Check 2		4.703	94.1
	Performance Check 3		4.423	88.5[a]
022812A	Performance Check 1	5	5.341	107
	Performance Check 2		5.047	101
	Performance Check 3		4.952	99.0
052212A	Performance Check 1	5	5.048	101
	Performance Check 2		5.024	100
	Performance Check 3		5.115	102

[a] This data point failed to meet acceptance criterion for recovery (±10%).

Table 3 **Calibration Curve Results**

Analytical Run	Standard Identification	Nominal Concentration (ng/mL)	Calculated Concentration (ng/mL)	%Recovery	Slope	y-intercept	Coefficient of Determination (R^2)
080710A	Standard 1	0.500	0.495	99.1	199000	1400	0.9998
	Standard 2	1.00	1.008	101			
	Standard 3	2.50	2.518	101			
	Standard 4	5.00	5.004	100			
	Standard 5	7.50	7.367	98.2			
	Standard 6	10.0	10.106	101			
081410A	Standard 1	0.500	0.507	101	196000	1760	0.9996
	Standard 2	1.00	1.007	101			
	Standard 3	2.50	2.465	98.6			
	Standard 4	5.00	4.936	98.7			
	Standard 5	7.50	7.393	98.6			
	Standard 6	10.0	10.191	102			
082110A	Standard 1	0.500	0.492	98.4	187000	8730	1.0000
	Standard 2	1.00	1.005	101			
	Standard 3	2.50	2.525	101			
	Standard 4	5.00	5.048	101			
	Standard 5	7.50	7.442	99.2			
	Standard 6	10.0	9.987	99.9			
082710A	Standard 1	0.500	0.497	99.4	182000	7190	0.9998
	Standard 2	1.00	1.012	101			
	Standard 3	2.50	2.468	98.7			
	Standard 4	5.00	5.086	102			
	Standard 5	7.50	7.388	98.5			
	Standard 6	10.0	10.050	100			

Table 3 **Calibration Curve Results**

Analytical Run	Standard Identification	Nominal Concentration (ng/mL)	Calculated Concentration (ng/mL)	%Recovery	Slope	y-intercept	Coefficient of Determination (R^2)
112910A	Standard 1	0.500	0.486	97.2	165000	18300	0.9998
	Standard 2	1.00	1.004	100			
	Standard 3	2.50	2.561	102			
	Standard 4	5.00	5.064	101			
	Standard 5	7.50	7.453	99.4			
	Standard 6	10.0	9.932	99.3			
022811A	Standard 1	0.500	0.524	105	65600	6990	0.9992
	Standard 2	1.00	0.939	93.9			
	Standard 3	2.50	2.581	103			
	Standard 4	5.00	4.885	97.7			
	Standard 5	7.50	7.407	98.8			
	Standard 6	10.0	10.164	102			
030111A	Standard 1	0.500	0.484	96.8	70600	667	0.9994
	Standard 2	1.00	1.022	102			
	Standard 3	2.50	2.483	99.3			
	Standard 4	5.00	5.119	102			
	Standard 5	7.50	7.602	101			
	Standard 6	10.0	9.789	97.9			
060611A	Standard 1	0.500	0.500	100	71770	2764.3	0.9991
	Standard 2	1.00	1.047	105			
	Standard 3	2.50	2.407	96.3			
	Standard 4	5.00	4.897	97.9			
	Standard 5	7.50	7.396	98.6			
	Standard 6	10.0	10.254	103			

Table 3 **Calibration Curve Results**

Analytical Run	Standard Identification	Nominal Concentration (ng/mL)	Calculated Concentration (ng/mL)	%Recovery	Slope	y-intercept	Coefficient of Determination (R^2)
060711A	Standard 1	0.500	0.543	109	96552	-770.204	0.9972
	Standard 2	1.00	0.986	98.6			
	Standard 3	2.50	2.344	93.8			
	Standard 4	5.00	4.838	96.8			
	Standard 5	7.50	7.296	97.3			
	Standard 6	10.0	10.493	105			
062611A	Standard 1	0.500	0.484	96.8	28788	939	0.9995
	Standard 2	1.00	1.011	101			
	Standard 3	2.50	2.612	104			
	Standard 4	5.00	4.875	97.5			
	Standard 5	7.50	7.469	99.6			
	Standard 6	10.0	10.049	100			
062611B	Standard 1	0.500	0.464	92.9	30220	800	0.9984
	Standard 2	1.00	1.082	108			
	Standard 3	2.50	2.543	102			
	Standard 4	5.00	4.752	95.0			
	Standard 5	7.50	7.681	102			
	Standard 6	10.0	9.978	99.8			
063011A	Standard 1	0.500	0.496	99.2	47359	2031	0.9992
	Standard 2	1.00	1.025	103			
	Standard 3	2.50	2.522	101			
	Standard 4	5.00	4.770	95.4			
	Standard 5	7.50	7.528	100			
	Standard 6	10.0	10.159	102			

Table 3 **Calibration Curve Results**

Analytical Run	Standard Identification	Nominal Concentration (ng/mL)	Calculated Concentration (ng/mL)	%Recovery	Slope	y-intercept	Coefficient of Determination (R^2)
082611A	Standard 1	0.500	0.544	109	29380	433	0.9968
	Standard 2	1.00	0.993	99.3			
	Standard 3	2.50	2.334	93.4			
	Standard 4	5.00	4.642	92.8			
	Standard 5	7.50	7.738	103			
	Standard 6	10.0	10.249	102			
083011A	Standard 1	0.500	0.495	98.9	30940	338	0.9996
	Standard 2	1.00	1.023	102			
	Standard 3	2.50	2.478	99.1			
	Standard 4	5.00	4.911	98.2			
	Standard 5	7.50	7.656	102			
	Standard 6	10.0	9.937	99.4			
113011A	Standard 1	0.500	0.523	105	47501.3	1779.26	0.9986
	Standard 2	1.00	0.984	98.4			
	Standard 3	2.50	2.498	99.9			
	Standard 4	5.00	4.713	94.3			
	Standard 5	7.50	7.521	100			
	Standard 6	10.0	10.261	103			
022712A	Standard 1	0.500	0.545	109	22909.6	-333.001	0.9987
	Standard 2	1.00	0.950	95.0			
	Standard 3	2.50	2.375	95.0			
	Standard 4	5.00	4.972	99.4			
	Standard 5	7.50	10.264	137[a]			
	Standard 6	10.0	10.158	102			

[a] This data point failed to meet acceptance criterion for recovery (±10%).

Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Table 3 **Calibration Curve Results**

Analytical Run	Standard Identification	Nominal Concentration (ng/mL)	Calculated Concentration (ng/mL)	%Recovery	Slope	y-intercept	Coefficient of Determination (R^2)
022812A	Standard 1	0.500	0.527	105	55836.3	1012.02	0.9968
	Standard 2	1.00	0.933	93.3			
	Standard 3	2.50	2.611	104			
	Standard 4	5.00	4.889	97.8			
	Standard 5	7.50	7.100	94.7			
	Standard 6	10.0	10.440	104			
052212A	Standard 1	0.500	0.499	99.8	315540	32553.1	0.9998
	Standard 2	1.00	1.022	102			
	Standard 3	2.50	2.467	98.7			
	Standard 4	5.00	4.943	98.9			
	Standard 5	7.50	7.434	99.1			
	Standard 6	10.0	10.135	101			

Table 4 Homogeneity Analysis of in Dosing Formulations – Week 1

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0.1	Top Replicate 1	0.01	0.00943	0.00940	94.3	94.0	1.40
	Top Replicate 2		0.00940		94.0		
	Middle Replicate 1		0.00914		91.4		
	Middle Replicate 2		0.00943		94.3		
	Bottom Replicate 1		0.00950		95.0		
	Bottom Replicate 2		0.00947		94.7		
1	Top Replicate 1	0.1	0.0935	0.0941	93.5	94.1	0.710
	Top Replicate 2		0.0946		94.6		
	Middle Replicate 1		0.0931		93.1		
	Middle Replicate 2		0.0946		94.6		
	Bottom Replicate 1		0.0947		94.7		
	Bottom Replicate 2		0.0941		94.1		
50	Top Replicate 1	5.0	4.87	4.77	97.5	95.3	1.98
	Top Replicate 2		4.87		97.4		
	Middle Replicate 1		4.77		95.4		
	Middle Replicate 2		4.69		93.8		
	Bottom Replicate 1		4.75		95.1		
	Bottom Replicate 2		4.64		92.8		
500	Top Replicate 1	50	45.6	46.6	91.2	93.2	1.63
	Top Replicate 2		45.7		91.5		
	Middle Replicate 1		47.2		94.4		
	Middle Replicate 2		46.8		93.6		
	Bottom Replicate 1		46.8		93.7		
	Bottom Replicate 2		47.4		94.9		

Table 5 Concentration Analysis of in Dosing Formulations – Week 1

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Replicate 1	0.0	0.000	0.000	NA	NA	NA
	Replicate 2		0.000		NA		
0.1	Replicate 1	0.01	0.00940	0.00932	94.0	93.2	1.24
	Replicate 2		0.00923		92.3		
1	Replicate 1	0.1	0.0929	0.0938	92.9	93.8	1.29
	Replicate 2		0.0947		94.7		
50	Replicate 1	5.0	4.71	4.80	94.3	96.1	2.64
	Replicate 2		4.89		97.9		
500	Replicate 1	50	45.0	45.1	90.1	90.3	0.332
	Replicate 2		45.2		90.5		

NA -Not Applicable/Not Available

Table 5 Concentration Analysis of in Dosing Formulations – Week 2

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Replicate 1	0.0	0.000	0.000	NA	NA	NA
	Replicate 2		0.000		NA		
0.1	Replicate 1	0.01	0.0107	0.01056	107	106	2.01
	Replicate 2		0.0104		104		
1	Replicate 1	0.1	0.0974	0.0986	97.4	98.7	1.79
	Replicate 2		0.0999		99.9		
50	Replicate 1	5.0	4.79	4.81	95.7	96.1	0.589
	Replicate 2		4.83		96.5		
500	Replicate 1	50	48.2	48.0	96.4	96.0	0.589
	Replicate 2		47.8		95.6		

NA -Not Applicable/Not Available

Table 5 Concentration Analysis of in Dosing Formulations – Week 3

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Replicate 1	0.0	0.000	0.000	NA	NA	NA
	Replicate 2		0.000		NA		
0.1	Replicate 1	0.01	0.00973	0.00967	97.3	96.7	0.877
	Replicate 2		0.00961		96.1		
1	Replicate 1	0.1	0.0946	0.0934	94.6	93.4	1.82
	Replicate 2		0.0922		92.2		
50	Replicate 1	5.0	4.78	4.78	95.6	95.5	0.148
	Replicate 2		4.77		95.4		
500	Replicate 1	50	45.7	45.7	91.5	91.4	0.155
	Replicate 2		45.7		91.3		

NA -Not Applicable/Not Available

Table 5 Concentration Analysis of in Dosing Formulations – Week 4

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Replicate 1	0.0	0.000	0.000	NA	NA	NA
	Replicate 2		0.000		NA		
0.1	Replicate 1	0.01	0.00950	0.00945	95.0	94.5	0.748
	Replicate 2		0.00940		94.0		
1	Replicate 1	0.1	0.0945	0.0936	94.5	93.6	1.44
	Replicate 2		0.0926		92.6		
50	Replicate 1	5.0	4.75	4.75	95.1	95.1	0.00
	Replicate 2		4.76		95.1		
500	Replicate 1	50	45.8	45.2	91.7	90.5	1.95
	Replicate 2		44.6		89.2[a]		

NA -Not Applicable/Not Available
[a] This data point is not within ±10 of the nominal concentration.

Table 5 Concentration Analysis of in Dosing Formulations – Week 17

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Replicate 1	0.0	0.000	0.000	NA	NA	NA
	Replicate 2		0.000		NA		
0.1	Replicate 1	0.01	0.00997	0.00967	99.7	96.7	4.39
	Replicate 2		0.00937		93.7		
1	Replicate 1	0.1	0.0960	0.0931	96.0	93.2	4.33
	Replicate 2		0.0903		90.3		
50	Replicate 1	5.0	4.73	4.66	94.7	93.2	2.35
	Replicate 2		4.58		91.6		
500	Replicate 1	50	47.2	47.4	94.4	94.9	0.671
	Replicate 2		47.7		95.3		

NA -Not Applicable/Not Available

Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Table 5 Concentration Analysis of in Dosing Formulations – Week 30

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Replicate 1	0.0	0.000	0.000	NA	NA	NA
	Replicate 2		0.000		NA		
0.1	Replicate 1	0.01	0.00937	0.00971	93.7	97.4	5.30
	Replicate 2		0.01006		101		
1	Replicate 1	0.1	0.09135	0.0899	91.3	89.9	2.20
	Replicate 2		0.08850		88.5[a]		
50	Replicate 1	5.0	4.01	4.48	80.3[a]	89.7	8.06[b]
	Replicate 2		4.50		89.9		
	Backup Replicate 1[c]		4.90		97.9		
	Backup Replicate 2[c]		4.53		90.7		
500	Replicate 1	50	43.3	44.1	86.5	88.3[d]	4.11
	Replicate 2		42.6		85.1		
	Backup Replicate 1[c]		44.0		88.1		
	Backup Replicate 2[c]		46.7		93.4		

NA -Not Applicable/Not Available
[a] This data point is not within ±10 of the nominal concentration.
[b] These data failed to meet acceptance criterion for relative standard deviation (≤5%).
[c] These data are the result of backup sample analysis conducted due to the original data failing to meet acceptance criterion for recovery (±10%).
[d] These data failed to meet acceptance criterion for recovery (±10%).

Table 5 Concentration Analysis of in Dosing Formulations – Week 44

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Replicate 1	0.0	0.000	0.000	NA	NA	NA
	Replicate 2		0.000		NA		
0.1	Replicate 1	0.01	0.02034	0.02	203	208[d]	3.34
	Replicate 2		0.02061		206		
	Backup Replicate 1[c]		0.02178		218		
	Backup Replicate 2[c]		0.02043		204		
0.1	Top Replicate 1	0.01	0.02179	0.02077	218	208[d]	5.04
	Top Replicate 2		0.02148		215		
	Backup Top Replicate 1[c]		0.02017		202		
	Backup Top Replicate 2[c]		0.01965		196		
0.1	Middle Replicate 1	0.01	0.02135	0.0203	213	203[d]	3.66
	Middle Replicate 2		0.02018		202		
	Backup Middle Replicate 1[c]		0.02015		202		
	Backup Middle Replicate 2[c]		0.01948		195		
0.1	Bottom Replicate 1	0.01	0.02051	0.02	205	208[d]	1.20
	Bottom Replicate 2		0.02108		211		
	Backup Bottom Replicate 1[c]		0.02077		208		
	Backup Bottom Replicate 2[c]		0.02069		207		

NA -Not Applicable/Not Available
[c] These data are the result of backup sample analysis conducted due to the original data failing to meet acceptance criterion for recovery (±10%).
[d] These data failed to meet acceptance criterion for recovery (±10%).

Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Table 5 Concentration Analysis of in Dosing Formulations – Week 44

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
1	Replicate 1	0.1	0.08210	0.08	82.1	81.3[d]	2.05
	Replicate 2		0.08322		83.2		
	Backup Replicate 1[c]		0.07958		79.6		
	Backup Replicate 2[c]		0.08024		80.2		
50	Replicate 1	5.0	3.78928	4.05	75.8	81.1[d]	5.49[b]
	Replicate 2		3.94909		79.0		
	Backup Replicate 1[c]		4.21909		84.4		
	Backup Replicate 2[c]		4.25504		85.1		
500	Replicate 1	50	40.56206	41.5	81.1	82.9[d]	2.05
	Replicate 2		41.90355		83.8		
	Backup Replicate 1[c]		40.95509		81.9		
	Backup Replicate 2[c]		42.39370		84.8		

NA -Not Applicable/Not Available
[b] These data failed to meet acceptance criterion for relative standard deviation (≤5%).
[c] These data are the result of backup sample analysis conducted due to the original data failing to meet acceptance criterion for recovery (±10%).
[d] These data failed to meet acceptance criterion for recovery (±10%).

Table 5 Concentration Analysis of in Dosing Formulations – Week 47

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Backup Replicate 3[e]	0.0	0.000	0.000	NA	NA	NA
	Backup Replicate 4[e]		0.000		NA		
0.1	Backup Replicate 3[e]	0.01	0.00882	0.00899	88.2[a]	89.9	2.60
	Backup Replicate 4[e]		0.00915		91.5		
1	Backup Replicate 3[e]	0.1	0.0844	0.0846	84.4	84.6[d]	0.251
	Backup Replicate 4[e]		0.0847		84.7		
50	Backup Replicate 3[e]	5.0	4.33	4.40	86.6	88.1[d]	2.41
	Backup Replicate 4[e]		4.48		89.6		
500	Backup Replicate 3[e]	50	44.4	45.2	88.8[a]	90.5	2.58
	Backup Replicate 4[e]		46.1		92.1		

NA -Not Applicable/Not Available

[a] This data point is not within ±10 of the nominal concentration.

[d] These data failed to meet acceptance criterion for recovery (±10%).

[e] These data are the result of backup sample analysis conducted due to the original and initial backup sample data failing to meet acceptance criterion for calibration standards, performance check standards, and/or recovery (±10%).

Table 5 Concentration Analysis of in Dosing Formulations – Week 48

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Replicate 1	0.0	0.000	0.000	NA	NA	NA
	Replicate 2		0.000		NA		
0.1	Replicate 1	0.01	0.00980	0.00891	98.0	89.1[d]	7.28
	Replicate 2		0.00896		89.6		
	Backup Replicate 1[f]		0.00833		83.3		
	Backup Replicate 2[f]		0.00855		85.5		
1	Replicate 1	0.1	0.0943	0.0914	94.3	91.4	4.57
	Replicate 2		0.0884		88.4[a]		
50	Replicate 1	5.0	4.57	4.58	91.4	91.6	0.309
	Replicate 2		4.59		91.8		
500	Replicate 1	50	45.2	46.1	90.4	92.3	2.84
	Replicate 2		47.0		94.1		

NA -Not Applicable/Not Available

[a] This data point is not within ±10 of the nominal concentration.

[d] These data failed to meet acceptance criterion for recovery (±10%).

[f] These data are the result of backup sample analysis conducted due to the original data resulting in a relative standard deviation value that was inconsistent with the previous sample analysis runs.

Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Table 5 Concentration Analysis of in Dosing Formulations – Week 56

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Replicate 1	0.0	0.000	0.000	NA	NA	NA
	Replicate 2		0.000		NA		
0.1	Replicate 1	0.01	0.00852	0.00869	85.2	86.9[d]	2.10
	Replicate 2		0.00858		85.8		
	Backup Replicate 1[c]		0.00893		89.3		
	Backup Replicate 2[c]		0.00872		87.2		
1	Replicate 1	0.1	0.08936	0.0881	89.4	88.1[d]	2.32
	Replicate 2		0.08739		87.4		
	Backup Replicate 1[c]		0.08550		85.5		
	Backup Replicate 2[c]		0.09004		90.0		
50	Replicate 1	5.0	4.44808	4.51	89.0[a]	90.3	1.96
	Replicate 2		4.57281		91.5		
500	Replicate 1	50	45.06284	45.6	90.1	91.2	1.63
	Replicate 2		46.10599		92.2		

NA -Not Applicable/Not Available
[a] This data point is not within ±10 of the nominal concentration.
[c] These data are the result of backup sample analysis conducted due to the original data failing to meet acceptance criterion for recovery (±10%).
[d] These data failed to meet acceptance criterion for recovery (±10%).

Table 5 Concentration Analysis of in Dosing Formulations – Week 69

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Replicate 1	0.0	0.000	0.000	NA	NA	NA
	Replicate 2		0.000		NA		
0.1	Replicate 1	0.01	0.0101	0.0101	101	101	0.00
	Replicate 2		0.0101		101		
1	Replicate 1	0.1	0.0882	0.0941	88.2[a]	94.1	8.80
	Replicate 2		0.0999		99.9		
50	Replicate 1	5.0	4.97	4.77	99.3	95.3	5.94
	Replicate 2		4.57		91.3		
500	Replicate 1	50	46.7	48.1	93.3	96.1	4.12
	Replicate 2		49.5		98.9		

NA -Not Applicable/Not Available
[a] This data point is not within ±10 of the nominal concentration.

Table 5 Concentration Analysis of in Dosing Formulations – Week 82

Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Replicate 1	0.0	0.000	0.000	NA	NA	NA
	Replicate 2		0.000		NA		
0.1	Replicate 1	0.01	0.0079	0.00822	78.7	82.2[d]	3.87
	Replicate 2		0.0081		80.9		
	Backup Replicate 1[g]		0.0086		86.2		
	Backup Replicate 2[g]		0.0083		82.8		
1	Replicate 1	0.1	0.0818	0.0828	81.8	82.9[d]	1.79
	Replicate 2		0.0839		83.9		
1	Backup Replicate 1[g]	0.1	0.0902	0.09806	90.2	98.6	12.0[h]
	Backup Replicate 2[g]		0.1069		107		
50	Replicate 1	5.0	4.6535	4.52	93.1	90.5	5.26
	Replicate 2		4.4145		88.3[a]		
	Backup Replicate 1[i]		4.7804		95.6		
	Backup Replicate 2[i]		4.2485		85.0[a]		
500	Replicate 1	50	43.2428	42.6	86.5	85.2[d]	1.31
	Replicate 2		42.1066		84.2		
	Backup Replicate 1[g]		42.1302		84.3		
	Backup Replicate 2[g]		42.8297		85.7		

NA -Not Applicable/Not Available

[a] This data point is not within ±10 of the nominal concentration.

[d] These data failed to meet acceptance criterion for recovery (±10%).

[g] These data are the result of backup sample analysis conducted due to the original data failing to meet acceptance criterion for recovery (±10%) and a failing performance check standard.

[h] These data failed to meet acceptance criterion for relative standard deviation (≤10%).

[i] These data are the result of backup sample analysis conducted due to a failing performance check standard in the original data.

Table 5 Concentration Analysis of in Dosing Formulations – Week 95

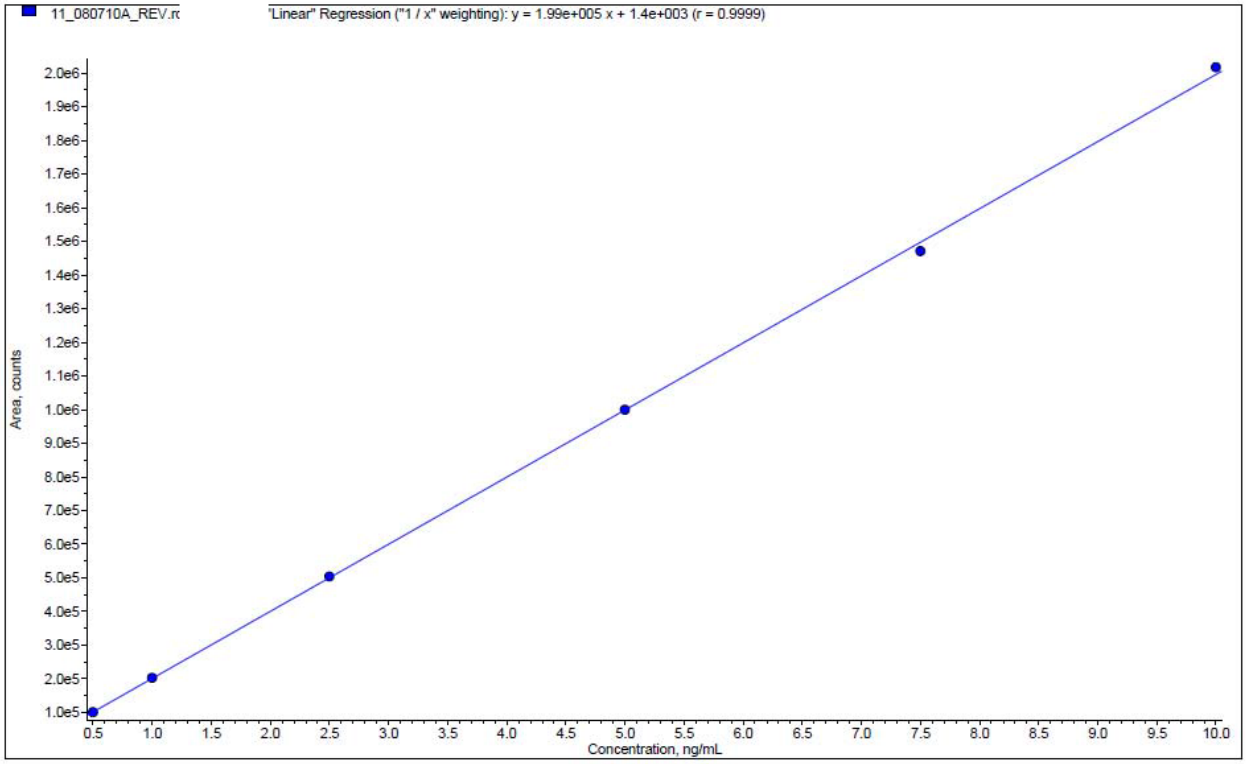
Dose Level (mg/kg/day)	Sample Identification	Nominal Concentration (mg/mL)	Calculated Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	%Recovery	Average %Recovery	%Relative Standard Deviation
0	Replicate 1	0.0	0.000	0.000	NA	NA	NA
	Replicate 2		0.000		NA		
0.1	Replicate 1	0.01	0.0095	0.00945	94.7	94.5	0.299
	Replicate 2		0.0094		94.3		
1	Replicate 1	0.1	0.0936	0.0909	93.6	90.9	4.20
	Replicate 2		0.0882		88.2		
50	Replicate 1	5.0	4.5015	4.57	90.0	91.4	2.17
	Replicate 2		4.6391		92.8		
500	Replicate 1	50	48.8988	49.5	97.8	98.9	1.57
	Replicate 2		50.0973		100		

NA -Not Applicable/Not Available

Figures

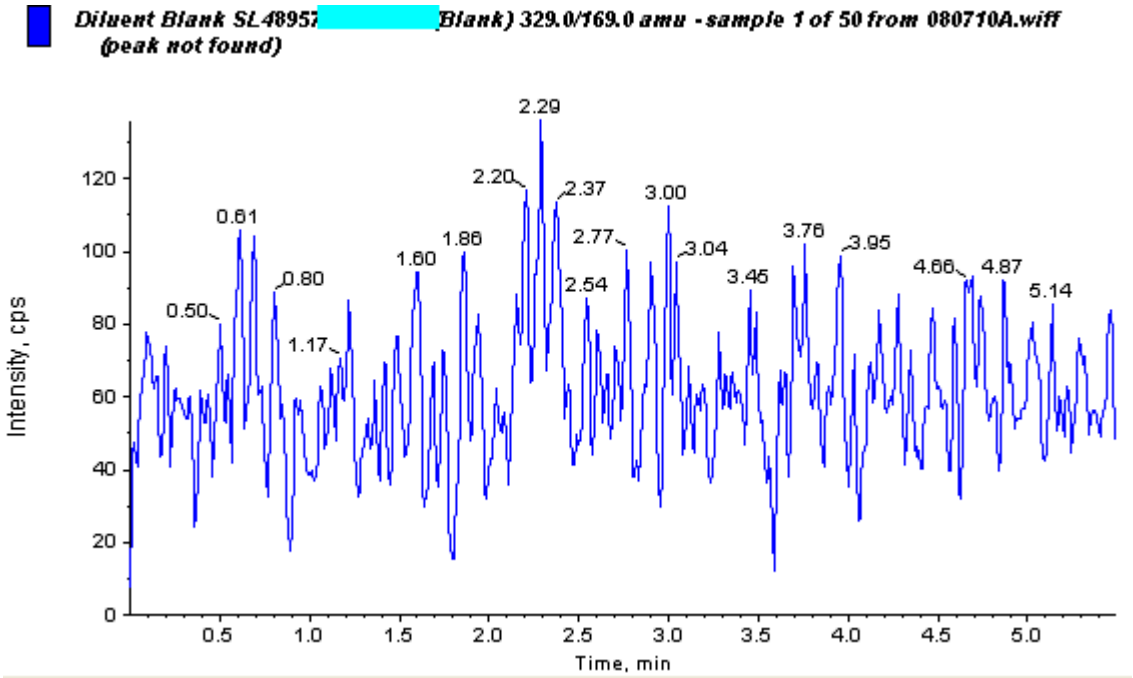
Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Figure 1 Representative Calibration Curve



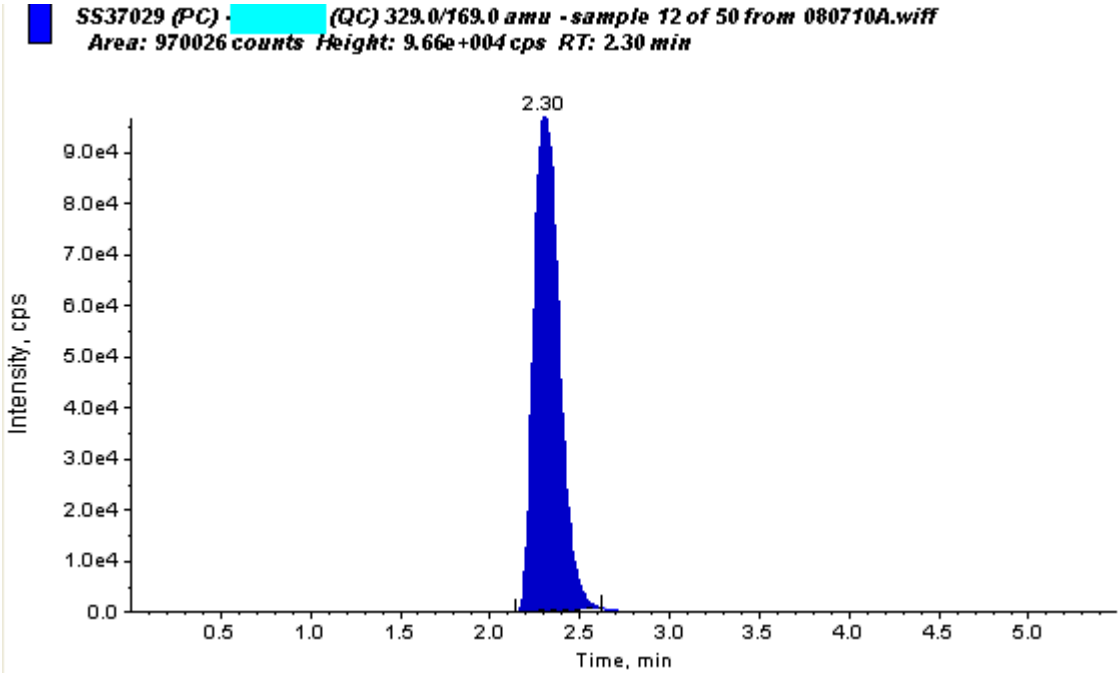
Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Figure 2 Representative Diluent Blank Injection



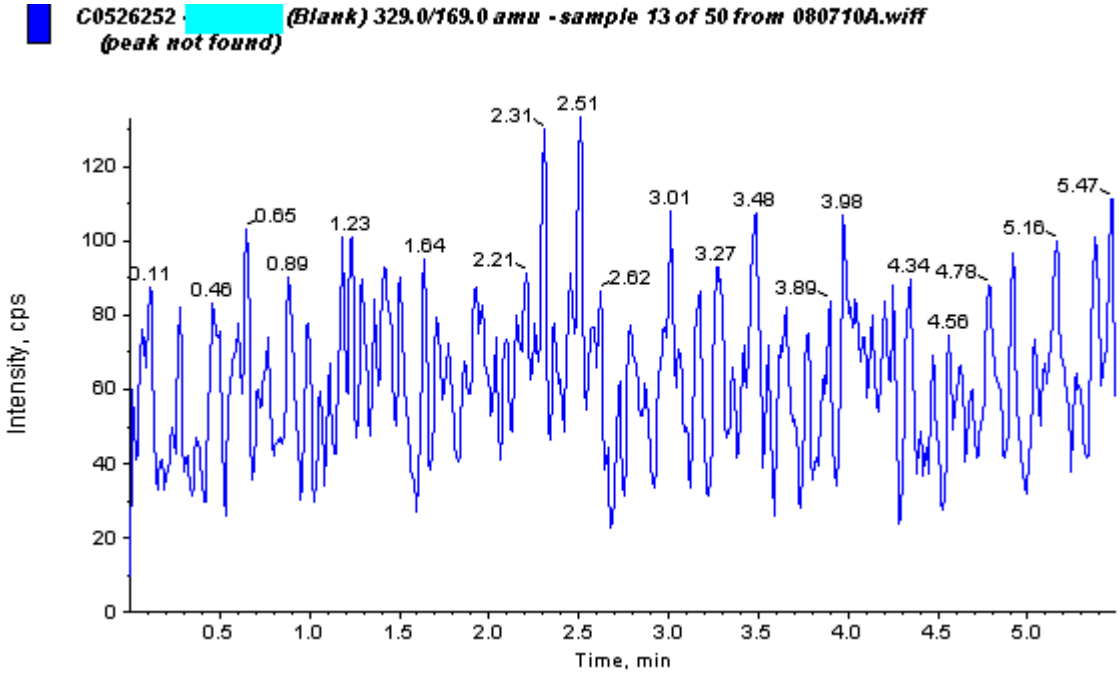
Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Figure 3 Representative Performance Check Injection



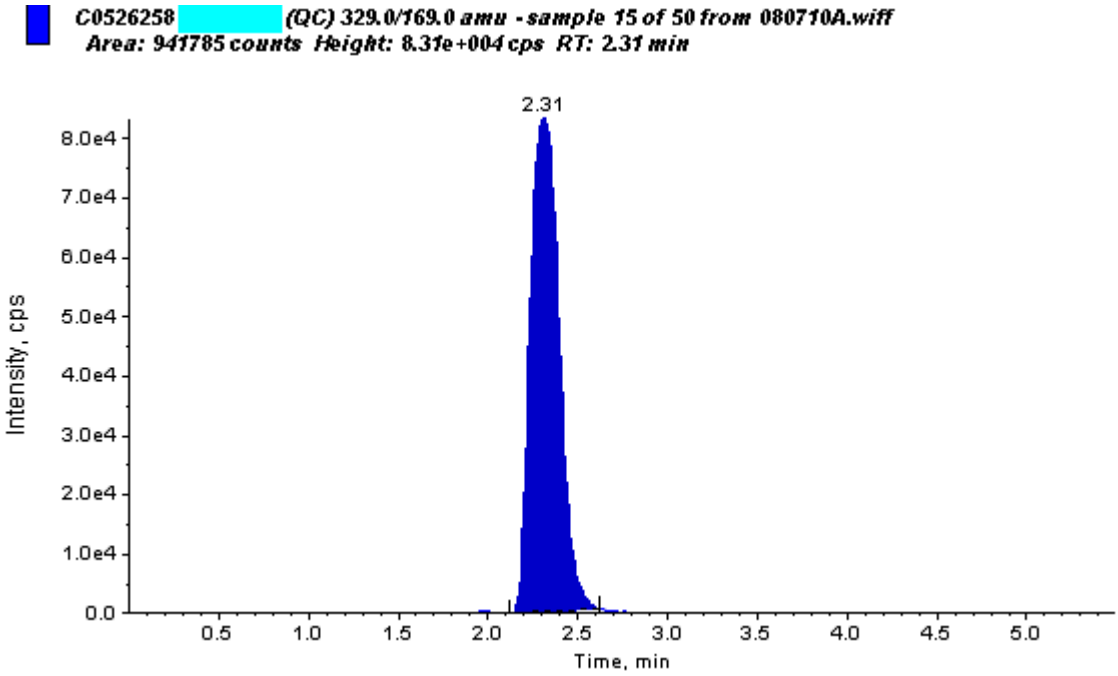
Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Figure 4 Representative 0 mg/mL Sample Injection



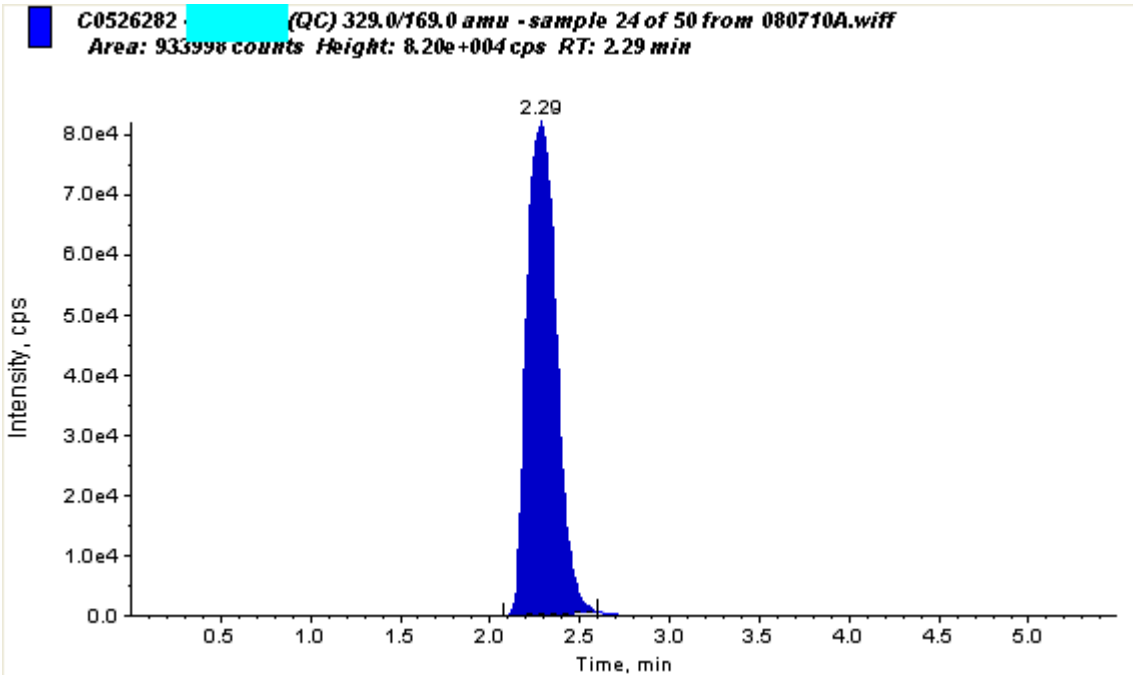
Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Figure 5 Representative 0.01 mg/mL Sample Injection



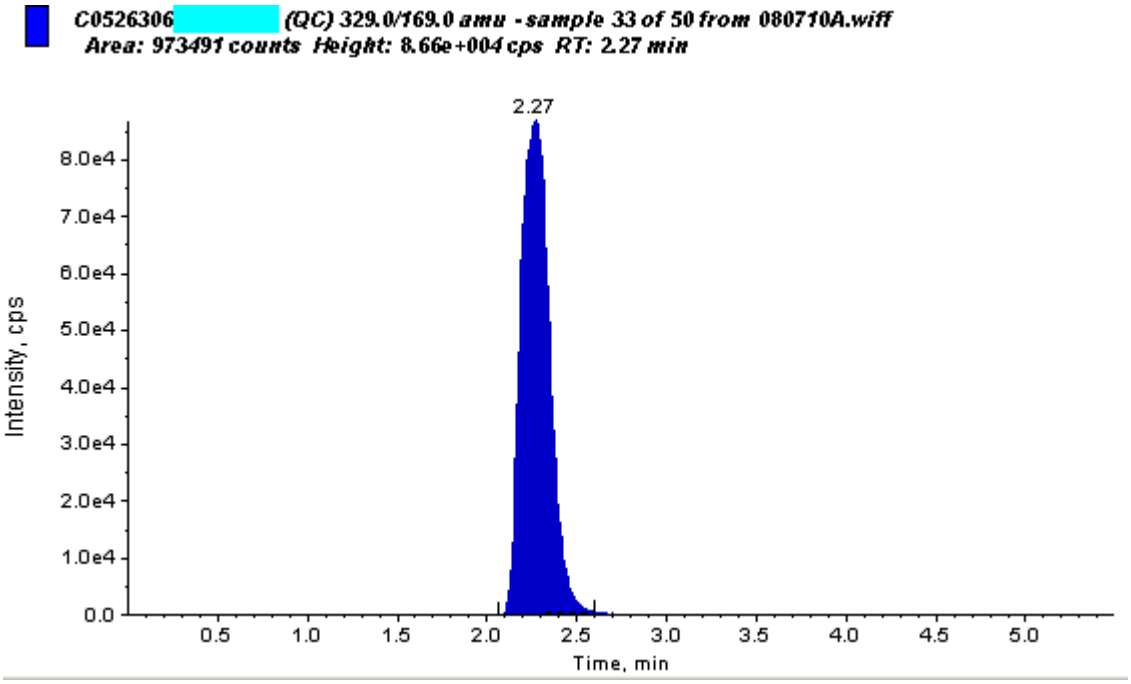
Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Figure 6 Representative 0.1 mg/mL Sample Injection



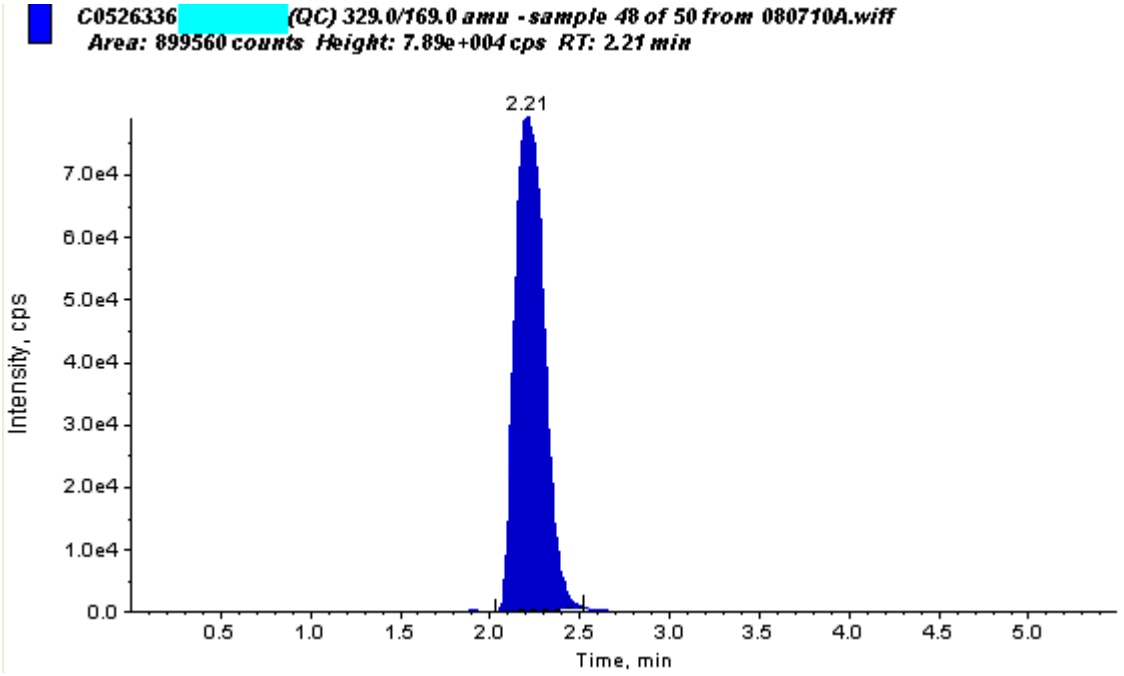
Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Figure 7 Representative 5.0 mg/mL Sample Injection



Study Number
Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Figure 8 Representative 50 mg/mL Sample Injection



Appendix A
Reference Standard Information

AN

Reference Standard Information

Date Received:	March 26, 2010
Supplier:	
Amount Received:	10 g
Label Identification:	
Lot Number:	
Correction Factor:	0.84 for purity
Expiration Date:	June 13, 2015
Storage:	Room temperature
Inventory Identification:	

CERTIFICATE OF ANALYSIS

This Certificate of Analysis fulfills the requirement for characterization of a test substance prior to a study subject to GLP regulations. It documents the identity and content of the test substance. Portions of this work were not conducted under EPA Good Laboratory Practice Standards (40 CFR 792).

Code Number	
Common Name	
Purity Percent	84%
Other Components	
Date of Analysis	June 13, 2008
Expiration Date	June 13, 2015
Instructions for storage	NRT&H
Reference	
Analysis performed at	

31-MAY-2011
Date

Revision #1: Revised COA expiration date based on compound stability assessment. 6/23/09
Revision #2: Revised COA expiration date based on compound stability assessment. 3/8/11

Appendix B
Analytical Method

ANALYTICAL METHOD

METHOD TITLE

DETERMINATION OF **IN DEIONIZED WATER DOSE FORMULATIONS BY LC-MS/MS**

APPROVAL

6/17/10
Date

EFFECTIVE DATE

06/17/2010

ANALYTICAL TESTING FACILITY

TABLE OF CONTENTS

1. INTRODUCTION

This analytical method is the result of validation activities performed at
The validation was commissioned by to support
Good Laboratory Practice (GLP) testing of formulated dosage forms containing

2. REFERENCES

3. TRAINING REQUIREMENTS

The analyst's training records must indicate the appropriate training requirements have been met. Documents applicable to the performance of the assay must be read prior to initiating activities related to the study.

4. METHOD LIMITATIONS

- The method is suitable to determine the concentration of in Deionized water at concentrations ranging from 0.005 to 75 mg/mL.
- Pre-processed samples are diluted such that post-processed samples contain at concentrations within the concentration range of the calibration curve.
- The response of in post-processed samples has been shown to be linear at concentrations ranging from 0.5 to 10 ng/mL.

5. PROCEDURAL NOTES

- Equivalent equipment or reagents may be substituted.
- Weights and volumes may be adjusted proportionately.
- Purity of the will be applied as directed by the Protocol.
- The method was validated by using a correction factor accounting for purity and moisture.
- The method was validated for solutions.

6. EQUIPMENT

LC-MS/MS System:	Agilent 1200 Series HPLC System OR Agilent 1100 Series HPLC System
Mass Spectrometer:	Applied Biosystems/MDS SCIEX API 4000 LC-MS/MS System
Data Acquisition System:	Applied Biosystems/MDS SCIEX Analyst 1.4.2 or equivalent OR Applied Biosystems /MDS SCIEX Analyst 1.4.1 or equivalent

Column: Zorbax SB-C8, 2.1 X 100 mm, 3.5 µm
Analytical balance: For use within its calibrated range 10 mg – 100 g
Microbalance: For use within its calibrated range 1 mg – 5 g
Class A volumetric glassware
Class A volumetric pipettes or calibrated mechanical pipettes
Vortex mixer

7. REAGENTS AND STANDARDS

Acetonitrile, HPLC Grade or better
Formic Acid, ACS Grade or better
Methanol, HPLC Grade or better
Water, HPLC Grade or better

8. PREPARATION OF SOLUTIONS

8.1. Mobile Phase A – 0.15% Formic Acid in Water

Combine 3 mL of formic acid and 1997 mL of HPLC grade water in an appropriately sized container. Mix the solution by inversion.

8.2. Mobile Phase B – Acetonitrile

8.3. Diluent – 50:50 Methanol: Water

Combine 1000 mL of methanol, and 1000 mL of HPLC grade water in an appropriately sized container. Mix the solution by inversion.

8.4. Needle Wash –Methanol

9. PREPARATION OF STANDARDS

9.1. Standard Stock (~100 µg/mL)

Transfer an equivalent of 10 mg ± 0.5 mg of into a 100 mL volumetric flask. Dilute to volume with Methanol to obtain an approximate concentration 100 µg/mL of Mix by appropriate means.

Note: The mass of the material may be adjusted to account for factors such as purity, salt, etc.

9.2. Intermediate Standards (~1000 ng/mL and ~100 ng/mL)

Transfer approximately 1 mL of standard stock into a 100 mL volumetric flask. Dilute to volume with Methanol to obtain an approximate concentration 1000 ng/mL of Mix by appropriate means.

Transfer approximately 10 mL of 1000 ng/mL intermediate standard into a 100 mL volumetric flask. Dilute to volume with Methanol to obtain an approximate concentration 100 ng/mL of Mix by appropriate means.

Note: The volume of the standard may be adjusted to account for factors such as purity, etc.

9.3. Calibration Standards (ng/mL)

The following table describes the dilution scheme for the calibration standards. Dilute the solution to volume with 50:50 Methanol:Water and mix by appropriate means.

Standard ID	Intermediate Standard Concentration (ng/mL)	Intermediate Standard Aliquot (mL)	Dilution Volume (mL)	Final Conc. (ng/mL)
Standard 1	100	0.05	10.0	0.5
Standard 2	100	0.1	10.0	1.0
Standard 3	100	0.25	10.0	2.5
Standard 4	100	0.5	10.0	5.0
Standard 5	100	0.75	10.0	7.5
Standard 6	100	1.0	10.0	10

9.4. SST Standard Stock (~100 µg/mL)

Transfer an equivalent of 10 mg ± 0.5 mg of into a 100 mL volumetric flask. Dilute to volume with Methanol to obtain an approximate concentration 100 µg/mL of Mix by appropriate means.

Note: The mass of the material may be adjusted to account for factors such as purity, salt, etc.

9.5. Intermediate SST Standards (~1000 ng/mL and ~100 ng/mL)

Transfer approximately 1 mL of SST standard stock into a 100 mL volumetric flask. Dilute to volume with Methanol to obtain an approximate concentration 1000 ng/mL of Mix by appropriate means.

Transfer approximately 10 mL of 1000 ng/mL intermediate SST standard into a 100 mL volumetric flask. Dilute to volume with Methanol to obtain an approximate concentration 100 ng/mL of Mix by appropriate means.

Note: The volume of the standard may be adjusted to account for factors such as purity, etc.

9.6. SST Standard (5 ng/mL)

Transfer 0.5 mL of the 100 ng/mL intermediate SST standard to a 10 mL volumetric flask. Dilute the solution to volume with 50:50 Methanol:Water and mix by appropriate means.

10. SAMPLE PROCESSING PROCEDURES

10.1. Control Vehicle Samples

Dilute the control vehicle samples with 50:50 Methanol:Water as indicated in the following table. Alternate dilution schemes may be used as long as a dilution factor of 1000 is maintained.

Initial Sample Conc. (mg/mL)	Sample Aliquot (mL)	Dilution Volume (mL)	Dilution Factor	Final Conc. (mg/mL)
0.00	0.01	10.0	1000	0.00

10.2. Formulation Samples

Dilute the pre-processed samples with 50:50 Methanol:Water such that the final concentration of the in the post-processed sample is within the concentration range of the calibration curve. Mix the post-processed sample by appropriate means. Examples of feasible sample dilutions are shown in the following table(s).

Initial Sample Conc. (mg/mL)	Primary Dilution		Secondary Dilution		Third Dilution			
	Sample Aliquot (mL)	Dilution Volume (mL)	Aliquot Volume (mL)	Final Volume (mL)	Aliquot Volume (mL)	Final Volume (mL)	Dilution Factor	Final Conc. (ng/mL)
0.005	0.01	10.0	NA	NA	NA	NA	1000	5
0.5	0.1	10.0	0.01	10.0	NA	NA	100,000	5
75	0.5	10.0	0.01	10.0	0.01	10.0	20,000,000	3.75

11. SYSTEM SUITABILITY

11.1. Blank Injection

The potential for interference to the assay must be evaluated by performing injections of the diluent. A blank injection must be performed prior to any other system suitability injections. A second blank injection will be made immediately following the last (highest concentration) injection of the calibration standard. Additional diluent blanks may be made prior to injection of vehicle samples to minimize the affect of potential carryover.

Acceptance Criterion

The initial blank injection and any diluent blank injections made immediately prior to study samples must not contain any peak(s) within the retention-time-region of the analyte peak having a total area response less than 20% of the response of the lowest standard.

11.2. SST Injections

The SST standard injections must be performed immediately following the first blank injection. A minimum of three replicate-injections of the SST standard are examined with respect to peak area, peak resolution, peak symmetry, and chromatographic performance.

Acceptance Criteria

Injection Repeatability (Peak Area %RSD) ≤10%
Signal to Noise ≥ 100

11.3. Calibration Standard Injections

A minimum of five of six calibration standards must be used to generate the calibration curve. If the lowest or highest calibration standard is excluded from the regression, sample results outside the acceptable range will not be reported.

Acceptance Criterion

The Percent Recovery (PR) of each of the calibration standards must be 100 ±10%, with respect to the calibration standard nominal concentration. The Coefficient of Determination (R^2) value must be ≥0.990.

11.4. Performance Check Injections

System performance will be monitored throughout each analysis by periodically injecting the SST Standard, which will serve as performance check standards. The performance check standards must be injected so that no more than 10 samples are bracketed by performance check standards. The calculated concentration of each performance check standard is determined using the calibration curve. Samples will be considered valid if they are bracketed by two performance checks that meet the criterion.

Acceptance Criterion

The Percent Recovery (PR) for each performance check injection should be within 100 ±10% of the nominal concentration.

12. STABILITY

Solution/Sample	Storage Condition	Expiration Period
Mobile Phase A/Diluent	Ambient	1 year
Pre-processed Samples	Ambient	14 days
Post-processed Samples	Ambient	27 hours
Pre-processed Calibration Standards	Ambient	27 hours
Post-processed Standards	Ambient	27 hours
Stock Standards	Ambient	14 days

13. HPLC CONDITIONS

Mobile Phase A:	0.15% Formic Acid in Water
Mobile Phase B:	Acetonitrile
Elution Type:	Isocratic, 35% B
Run Time:	5.50 minutes
Flow Rate:	0.4 mL/min
Injection Volume:	15 µL
Needle Wash:	25 seconds
Column Temperature:	35°C
Autosampler Temperature:	Ambient
Column:	Zorbax SB-C8, 2.1 X 100 mm, 3.5 µm

13.1. MS/MS Conditions

Polarity:	Negative
Scan Type:	Multiple Reaction Monitoring (MRM)
Ionization Mode:	Turbo IonSpray
Precursor ion →	Product Ion: m/z: 329.0→169.0 (

Typical mass spectrometer parameter settings		
CUR	Curtain Gas	30
GS1	Gas 1	40
GS2	Gas 2	40
TEM	Temperature	400
IS	Ion Spray Voltage	-4200
CAD	Collision gas	3.0
DP	Declustering Potential	-20
EP	Entrance Potential	-10
CE	Collision cell entrance potential	-18
CXP	Collision cell exit potential	-10

The parameters above may be slightly modified to optimize system response. Actual parameters will be recorded in the data.

14. CALCULATIONS

14.1. Linear Regression

A linear least squares analysis of the calibration curve must be performed using a validated chromatographic software package. The calibration curve will be constructed by plotting the peak area of the calibration standards versus the concentration of the calibration standards using 1/X weighting. The linear regression equation is shown below:

$$y = (m)x + b$$

Where:

y = peak-area generated by each calibration standard
x = Concentration of the analyte in each calibration standard
m = Slope of the calibration curve
b = y-intercept of the calibration curve

14.2. Sample Concentration

The measured concentration of the analyte in the samples is determined using the calibration curve and solving for the x variable:

$$x = \frac{y - b}{m} \times d$$

Where:

y = peak-area generated by the sample
x = measured concentration of the analyte in each sample
m = slope of the calibration curve
b = y-intercept of the calibration curve
d = dilution factor

14.3. Percent Relative Standard Deviation (%RSD)

The %RSD is calculated as follows:

$$\%RSD = \frac{SD}{mean} \times 100$$

Where:

SD = standard deviation of replicate measurements
Mean = mean of the replicate measurements

14.4. Percent Recovery (PR)

The PR is calculated as follows:

$$PR = \frac{C_m}{C_n} \times 100$$

Where:

C_m = Calculated Concentration
C_n = Nominal Concentration

15. SAFETY

It is recommended that analysts read related MSDS information before proceeding with the analysis. Safety glasses and nitrile or latex gloves must be worn.

16. AM CHANGE HISTORY

Version 01 - New Method Effective 06/17/2010

17. ATTACHMENTS

Figure 1. Representative Chromatogram of a Diluent Injection

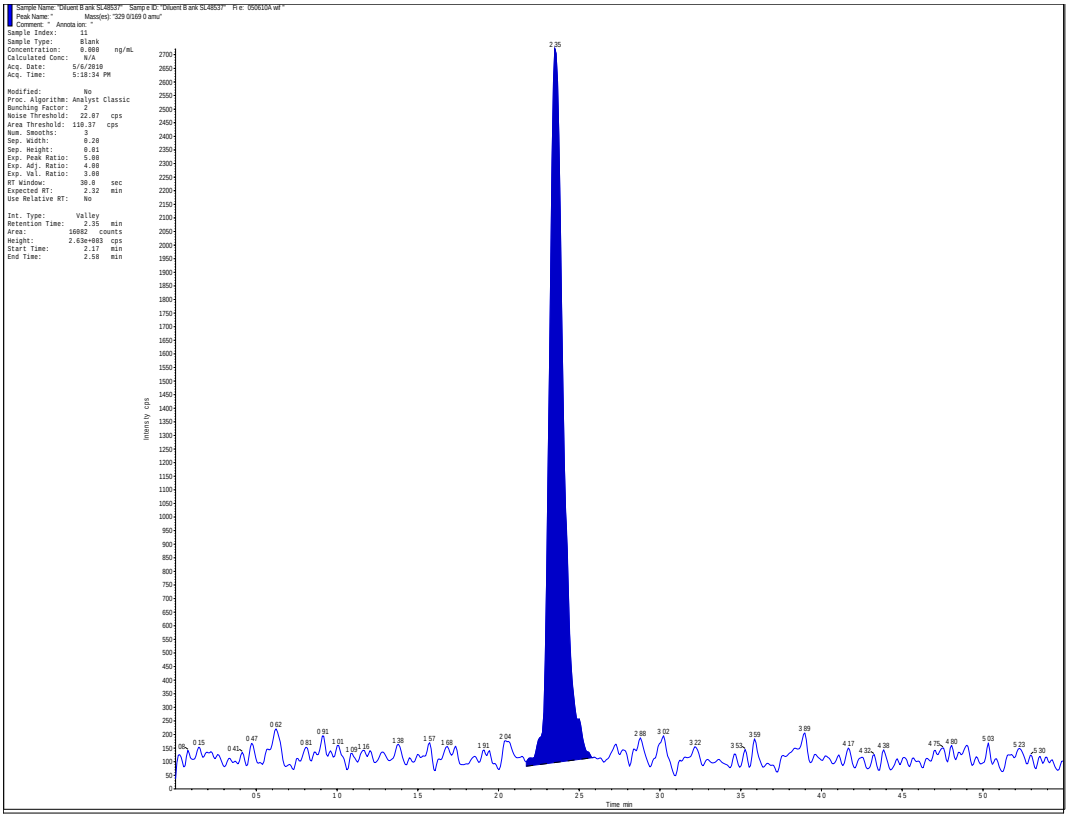


Figure 2. Representative Chromatogram of a Vehicle Injection

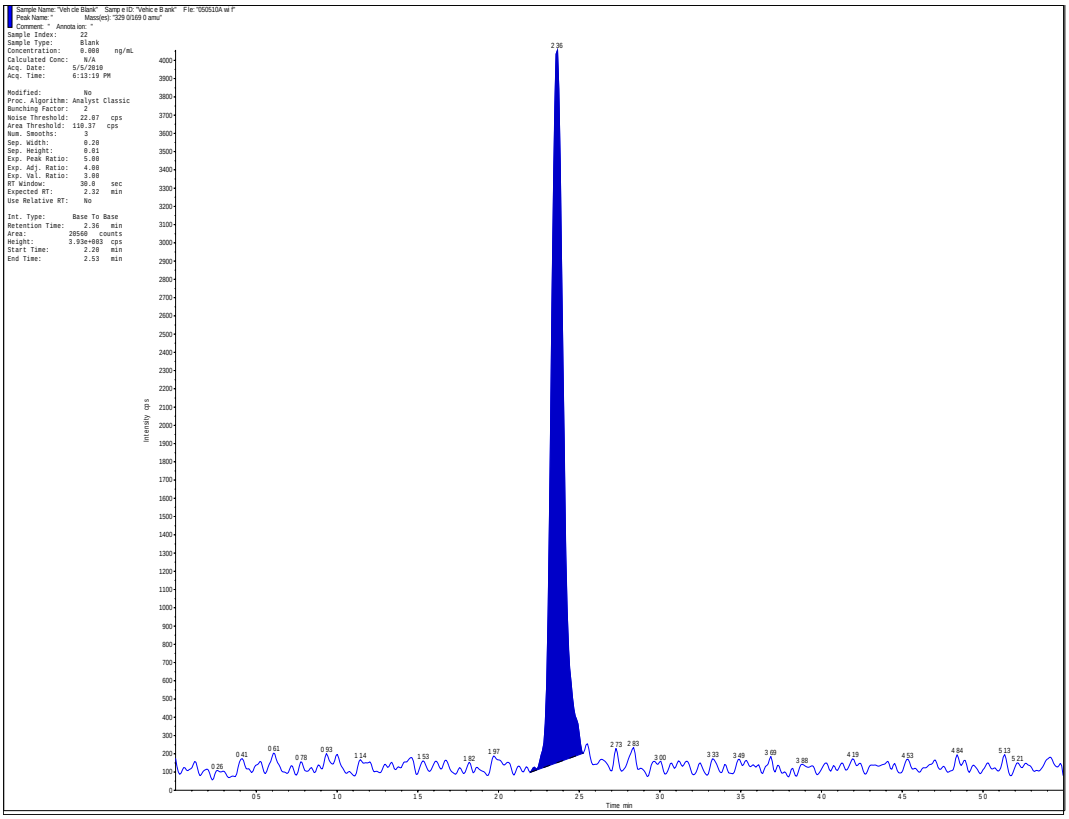


Figure 3. Representative Chromatogram of a QC Low Sample Injection

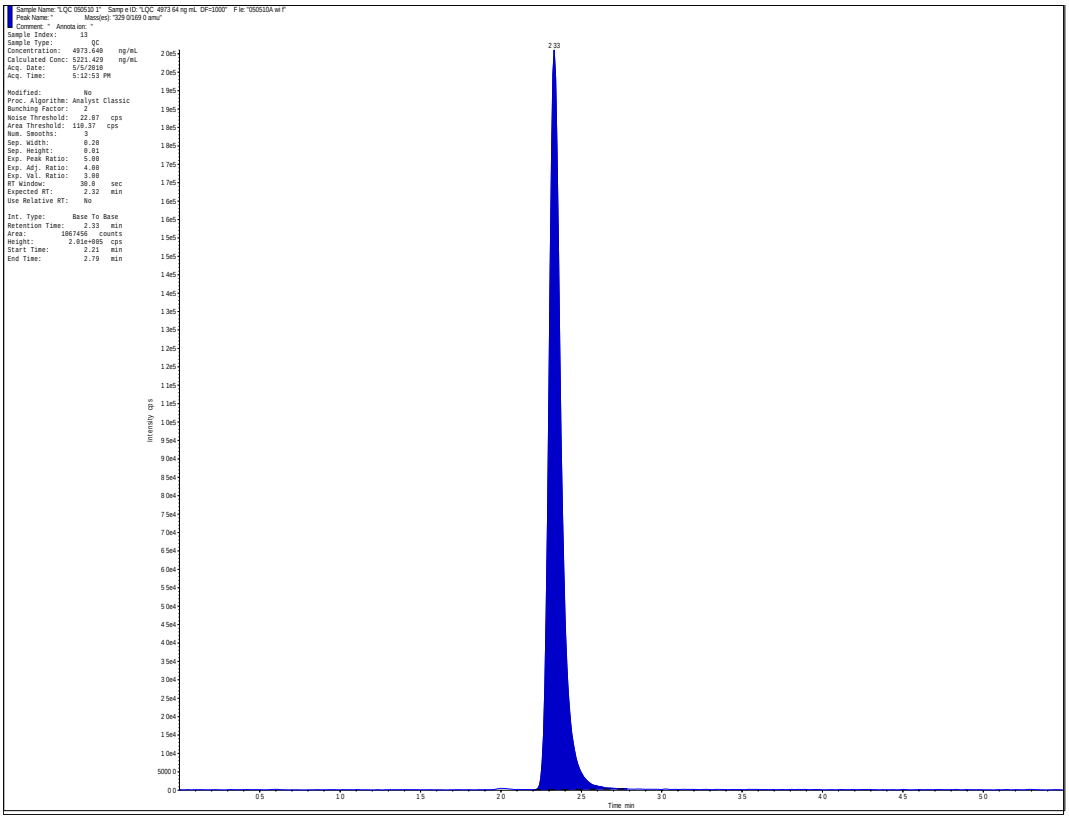
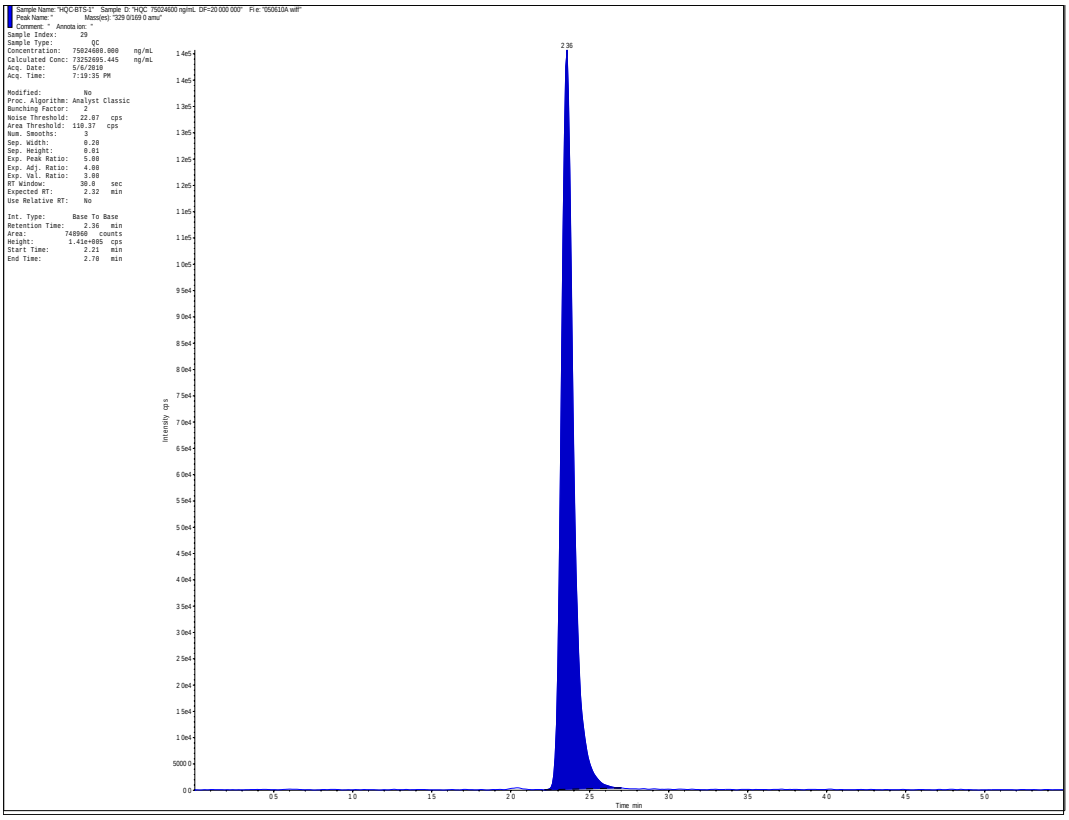


Figure 4. Representative Chromatogram of a QC High Sample Injection



Appendix C
Computer Systems

Computer Systems

The computer systems used during the conduct of this study are presented in the following table.

Computer Systems	
Analyst® v1.4:	Provides instrument control and data acquisition for API LC/MS/MS systems, and data reduction for API LC/MS/MS and HP LC/MS systems.
:	A comprehensive laboratory information management system used to manage data, including but not limited to: instrumentation, test articles, standards, samples, solutions, projects, controlled documents, and training.
eDocs v3:	In-house developed application for automated storage and retrieval information for archiveable materials (e.g., lab books, study data, wet tissues, slides, etc.).
MasterControl QAAD v8.0:	Electronic document management system.
docuBridge® v3:	A quality management system, consisting of the QAAD and QAADLink applications, used to automate the Quality Assurance process for regulatory compliance.
Microsoft® Office Professional 2003/2010:	Electronic publishing system.
	Suite of integrated productivity tools including word and data processing and communications software.

Additional information is available in the company document titled "Computer Systems Information."

Appendix C
Record of Animal Fate and Disposition

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - MALE

Group, Animal Number	Fate	Day
0 mg/kg/day		
1001	interim necropsy	369
1002	interim necropsy	369
1003	interim necropsy	369
1004	interim necropsy	369
1005	interim necropsy	369
1006	interim necropsy	370
1007	interim necropsy	370
1008	interim necropsy	370
1009	interim necropsy	370
1010	interim necropsy	370
1011	terminal necropsy	722
1012	found dead	635
1013	found dead	663
1014	terminal necropsy	722
1015	terminal necropsy	722
1016	euthanized *in extremis*	602
1017	euthanized *in extremis*	486
1018	euthanized *in extremis*	654
1019	euthanized *in extremis*	547
1020	found dead	546
1021	euthanized *in extremis*	688
1022	found dead	696
1023	found dead	614
1024	euthanized *in extremis*	645
1025	terminal necropsy	722
1026	terminal necropsy	722
1027	euthanized *in extremis*	439
1028	found dead	643
1029	terminal necropsy	722
1030	found dead	598
1031	terminal necropsy	722
1032	euthanized *in extremis*	458
1033	found dead	301
1034	euthanized *in extremis*	442
1035	terminal necropsy	722
1036	terminal necropsy	722
1037	found dead	628
1038	found dead	474
1039	euthanized *in extremis*	714

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - MALE

Group, Animal Number	Fate	Day
0 mg/kg/day		
1040	found dead	663
1041	terminal necropsy	722
1042	euthanized *in extremis*	623
1043	found dead	535
1044	found dead	307
1045	terminal necropsy	723
1046	found dead	196
1047	euthanized *in extremis*	482
1048	euthanized *in extremis*	380
1049	euthanized *in extremis*	597
1050	found dead	596
1051	euthanized *in extremis*	641
1052	euthanized *in extremis*	617
1053	found dead	448
1054	euthanized *in extremis*	687
1055	euthanized *in extremis*	602
1056	euthanized *in extremis*	404
1057	found dead	675
1058	euthanized *in extremis*	569
1059	found dead	191
1060	euthanized *in extremis*	698
1061	euthanized *in extremis*	502
1062	terminal necropsy	723
1063[r]	euthanized *in extremis*	686
1064	found dead	500
1065	euthanized *in extremis*	577
1066	found dead	474
1067	terminal necropsy	723
1068	terminal necropsy	723
1069	found dead	545
1070	euthanized *in extremis*	525
1071	euthanized *in extremis*	708
1072	found dead	692
1073	euthanized *in extremis*	666
1074	euthanized *in extremis*	386
1075	found dead	722
1076	terminal necropsy	723
1077	euthanized *in extremis*	722
1078	euthanized *in extremis*	611

[r] Replacement animal

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - MALE

Group, Animal Number	Fate	Day
0 mg/kg/day		
1079	euthanized *in extremis*	619
1080	found dead	693
0.1 mg/kg/day		
1081	interim necropsy	369
1082	interim necropsy	369
1083	interim necropsy	369
1084	interim necropsy	369
1085	interim necropsy	369
1086	interim necropsy	370
1087	interim necropsy	370
1088	interim necropsy	370
1089	interim necropsy	370
1090	interim necropsy	370
1091	terminal necropsy	722
1092	found dead	408
1093	terminal necropsy	722
1094	terminal necropsy	722
1095	found dead	507
1096	terminal necropsy	722
1097	terminal necropsy	722
1098	found dead	642
1099	terminal necropsy	722
1100	found dead	663
1101	found dead	388
1102	found dead	650
1103	found dead	140
1104	found dead	435
1105	euthanized *in extremis*	651
1106	found dead	294
1107	terminal necropsy	722
1108	euthanized *in extremis*	623
1109	terminal necropsy	722
1110	euthanized *in extremis*	687
1111	euthanized *in extremis*	322
1112	terminal necropsy	722
1113	euthanized *in extremis*	630
1114	euthanized *in extremis*	506
1115	euthanized *in extremis*	645

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - MALE

Group, Animal Number	Fate	Day
0.1 mg/kg/day		
1116	found dead	22
1117	euthanized *in extremis*	628
1118	euthanized *in extremis*	590
1119	found dead	354
1120	terminal necropsy	722
1121	euthanized *in extremis*	590
1122	terminal necropsy	723
1123	terminal necropsy	723
1124	terminal necropsy	723
1125	euthanized *in extremis*	701
1126	euthanized *in extremis*	687
1127	terminal necropsy	723
1128	euthanized *in extremis*	553
1129	euthanized *in extremis*	597
1130	euthanized *in extremis*	708
1131	found dead	451
1132	terminal necropsy	723
1133	found dead	634
1134	euthanized *in extremis*	711
1135	found dead	660
1136	euthanized *in extremis*	645
1137	found dead	533
1138	euthanized *in extremis*	694
1139	found dead	87
1140	terminal necropsy	723
1141	died after blood collection	408
1142	found dead	391
1143	terminal necropsy	723
1144	found dead	334
1145	euthanized *in extremis*	330
1146	found dead	527
1147	terminal necropsy	723
1148	euthanized *in extremis*	574
1149	euthanized *in extremis*	617
1150	terminal necropsy	723
1151	euthanized *in extremis*	587
1152	euthanized *in extremis*	512
1153	euthanized *in extremis*	625
1154	terminal necropsy	723

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - MALE

Group, Animal Number	Fate	Day
0.1 mg/kg/day		
1155	euthanized *in extremis*	251
1156	euthanized *in extremis*	569
1157	euthanized *in extremis*	713
1158	euthanized *in extremis*	628
1159	euthanized *in extremis*	708
1160	found dead	651
1 mg/kg/day		
1161	interim necropsy	369
1162	interim necropsy	369
1163	interim necropsy	369
1164	interim necropsy	369
1165	interim necropsy	369
1166	interim necropsy	370
1167	interim necropsy	370
1168	interim necropsy	370
1169	interim necropsy	370
1170	interim necropsy	370
1171	terminal necropsy	722
1172	euthanized *in extremis*	569
1173	euthanized *in extremis*	553
1174	found dead	308
1175	found dead	634
1176	terminal necropsy	722
1177	found dead	308
1178	terminal necropsy	722
1179	found dead	515
1180	terminal necropsy	722
1181	found dead	402
1182	found dead	450
1183	found dead	537
1184	euthanized *in extremis*	591
1185	found dead	552
1186	terminal necropsy	722
1187	found dead	549
1188	euthanized *in extremis*	602
1189	found dead	462
1190	euthanized *in extremis*	247
1191	euthanized *in extremis*	363

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - MALE

Group, Animal Number	Fate	Day
1 mg/kg/day		
1192	terminal necropsy	722
1193	terminal necropsy	722
1194	terminal necropsy	722
1195	euthanized *in extremis*	602
1196	euthanized *in extremis*	657
1197	found dead	467
1198	euthanized *in extremis*	628
1199	terminal necropsy	722
1200	found dead	679
1201	found dead	546
1202	euthanized *in extremis*	722
1203	found dead	303
1204	terminal necropsy	723
1205	found dead	537
1206	euthanized *in extremis*	552
1207	found dead	205
1208	found dead	510
1209	euthanized *in extremis*	619
1210	euthanized *in extremis*	686
1211	terminal necropsy	723
1212	terminal necropsy	723
1213	euthanized *in extremis*	624
1214	found dead	478
1215	found dead	491
1216	found dead	394
1217	euthanized *in extremis*	703
1218	terminal necropsy	723
1219	died prior to euthanasia	554
1220	died after dosing	680
1221	terminal necropsy	723
1222	found dead	481
1223	terminal necropsy	723
1224	euthanized *in extremis*	475
1225	terminal necropsy	723
1226	euthanized *in extremis*	538
1227	terminal necropsy	723
1228	found dead	403
1229	euthanized *in extremis*	664
1230	euthanized *in extremis*	260

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - MALE

Group, Animal Number	Fate	Day
1 mg/kg/day		
1231	found dead	425
1232	found dead	569
1233	euthanized *in extremis*	419
1234	found dead	413
1235	found dead	449
1236	euthanized *in extremis*	716
1237	euthanized *in extremis*	352
1238	euthanized *in extremis*	475
1239	euthanized *in extremis*	617
1240	terminal necropsy	723
50 mg/kg/day		
1241	interim necropsy	369
1242	interim necropsy	369
1243	interim necropsy	369
1244	interim necropsy	369
1245	interim necropsy	369
1246	interim necropsy	370
1247	interim necropsy	370
1248	interim necropsy	370
1249[r]	interim necropsy	370
1250	interim necropsy	370
1251	terminal necropsy	722
1252	terminal necropsy	722
1253	euthanized *in extremis*	610
1254	terminal necropsy	722
1255	died after blood collection	722
1256	found dead	456
1257	terminal necropsy	722
1258	found dead	673
1259	found dead	462
1260	died after blood collection	716
1261	terminal necropsy	722
1262	found dead	575
1263	euthanized *in extremis*	608
1264	euthanized *in extremis*	554
1265	found dead	506
1266	found dead	587
1267	found dead	628

[r] Replacement animal

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - MALE

Group, Animal Number	Fate	Day
50 mg/kg/day		
1268	found dead	395
1269	euthanized *in extremis*	646
1270	terminal necropsy	722
1271	found dead	722
1272	found dead	348
1273	euthanized *in extremis*	380
1274	euthanized *in extremis*	582
1275	found dead	545
1276	euthanized *in extremis*	596
1277	terminal necropsy	722
1278	found dead	614
1279	found dead	497
1280	found dead	722
1281	found dead	419
1282	euthanized *in extremis*	671
1283	terminal necropsy	722
1284	euthanized *in extremis*	352
1285	euthanized *in extremis*	432
1286	terminal necropsy	722
1287	terminal necropsy	722
1288	euthanized *in extremis*	617
1289	terminal necropsy	723
1290	euthanized *in extremis*	569
1291	found dead	720
1292	found dead	442
1293	found dead	623
1294	terminal necropsy	723
1295	terminal necropsy	723
1296	euthanized *in extremis*	407
1297	terminal necropsy	723
1298	euthanized *in extremis*	444
1299	euthanized *in extremis*	596
1300	euthanized *in extremis*	400
1301	found dead	635
1302	found dead	413
1303	found dead	612
1304	found dead	543
1305	euthanized *in extremis*	558
1306	found dead	423

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - MALE

Group, Animal Number	Fate	Day
50 mg/kg/day		
1307	found dead	639
1308	euthanized *in extremis*	708
1309	terminal necropsy	723
1310	euthanized *in extremis*	571
1311	terminal necropsy	723
1312	found dead	322
1313	euthanized *in extremis*	709
1314	euthanized *in extremis*	700
1315	terminal necropsy	723
1316	found dead	411
1317	euthanized *in extremis*	392
1318	euthanized *in extremis*	376
1319	terminal necropsy	723
1320	euthanized *in extremis*	439

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - FEMALE

Group, Animal Number	Fate	Day
0 mg/kg/day		
1321	found dead	349
1322	interim necropsy	369
1323	found dead	311
1324	interim necropsy	369
1325	interim necropsy	369
1326	interim necropsy	369
1327	interim necropsy	369
1328	interim necropsy	370
1329	interim necropsy	370
1330	interim necropsy	370
1331	interim necropsy	370
1332	interim necropsy	370
1333	terminal necropsy	705
1334	euthanized *in extremis*	666
1335	terminal necropsy	705
1336	euthanized *in extremis*	653
1337	euthanized *in extremis*	378
1338	euthanized *in extremis*	609
1339	terminal necropsy	705
1340	euthanized *in extremis*	691
1341	euthanized *in extremis*	250
1342	euthanized *in extremis*	476
1343	euthanized *in extremis*	505
1344	euthanized *in extremis*	411
1345	euthanized *in extremis*	596
1346	euthanized *in extremis*	407
1347	terminal necropsy	705
1348	found dead	616
1349	euthanized *in extremis*	469
1350	found dead	464
1351	found dead	495
1352	terminal necropsy	705
1353	terminal necropsy	705
1354	euthanized *in extremis*	635
1355	terminal necropsy	705
1356	euthanized *in extremis*	467
1357	terminal necropsy	705
1358	terminal necropsy	706
1359	euthanized *in extremis*	505

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - FEMALE

Group, Animal Number	Fate	Day
0 mg/kg/day		
1360	found dead	644
1361	found dead	654
1362	euthanized *in extremis*	639
1363	found dead	609
1364	euthanized *in extremis*	483
1365	terminal necropsy	706
1366	euthanized *in extremis*	639
1367	euthanized *in extremis*	617
1368	terminal necropsy	706
1369	euthanized *in extremis*	609
1370	terminal necropsy	706
1371	euthanized *in extremis*	334
1372	terminal necropsy	706
1373	euthanized *in extremis*	357
1374	terminal necropsy	706
1375	euthanized *in extremis*	462
1376	euthanized *in extremis*	604
1377	found dead	399
1378	found dead	514
1379	euthanized *in extremis*	455
1380	euthanized *in extremis*	363
1381	euthanized *in extremis*	464
1382	found dead	557
1383	found dead	550
1384	euthanized *in extremis*	638
1385	euthanized *in extremis*	659
1386	euthanized *in extremis*	616
1387	euthanized *in extremis*	532
1388	euthanized *in extremis*	453
1389	terminal necropsy	706
1390	euthanized *in extremis*	609
1391	euthanized *in extremis*	680
1392	terminal necropsy	706
1393	euthanized *in extremis*	610
1394	euthanized *in extremis*	677
1395	euthanized *in extremis*	428
1396	euthanized *in extremis*	485
1397	found dead	702
1398	euthanized *in extremis*	659

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - FEMALE

Group, Animal Number	Fate	Day
0 mg/kg/day		
1399	euthanized *in extremis*	354
1400	euthanized *in extremis*	623
1 mg/kg/day		
1401	interim necropsy	369
1402	interim necropsy	369
1403	interim necropsy	369
1404	interim necropsy	369
1405	interim necropsy	369
1406	interim necropsy	370
1407	interim necropsy	370
1408	interim necropsy	370
1409	interim necropsy	370
1410	interim necropsy	370
1411	euthanized *in extremis*	400
1412	euthanized *in extremis*	679
1413	found dead	605
1414	found dead	660
1415	found dead	687
1416	terminal necropsy	705
1417	found dead	626
1418	terminal necropsy	705
1419	terminal necropsy	705
1420	found dead	441
1421	euthanized *in extremis*	301
1422	euthanized *in extremis*	540
1423	euthanized *in extremis*	444
1424	terminal necropsy	705
1425	terminal necropsy	705
1426	euthanized *in extremis*	579
1427	found dead	507
1428	euthanized *in extremis*	569
1429	terminal necropsy	705
1430	terminal necropsy	705
1431	terminal necropsy	705
1432	terminal necropsy	705
1433	euthanized *in extremis*	544
1434	terminal necropsy	705
1435	terminal necropsy	705

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - FEMALE

Group, Animal Number	Fate	Day
1 mg/kg/day		
1436	euthanized *in extremis*	628
1437	terminal necropsy	706
1438	terminal necropsy	706
1439	euthanized *in extremis*	681
1440	terminal necropsy	706
1441	euthanized *in extremis*	523
1442	euthanized *in extremis*	596
1443	euthanized *in extremis*	617
1444	euthanized *in extremis*	541
1445	euthanized *in extremis*	385
1446	found dead	479
1447	terminal necropsy	706
1448	found dead	609
1449	found dead	516
1450	terminal necropsy	706
1451	euthanized *in extremis*	644
1452	euthanized *in extremis*	562
1453	euthanized *in extremis*	420
1454	terminal necropsy	706
1455	found dead	604
1456	found dead	590
1457	euthanized *in extremis*	568
1458	euthanized *in extremis*	275
1459	euthanized *in extremis*	521
1460	terminal necropsy	706
1461	euthanized *in extremis*	510
1462	euthanized *in extremis*	410
1463	euthanized *in extremis*	617
1464	died prior to euthanasia	554
1465	found dead	552
1466	found dead	211
1467	terminal necropsy	706
1468	died prior to euthanasia	551
1469	terminal necropsy	706
1470	euthanized *in extremis*	439
1471	terminal necropsy	706
1472	euthanized *in extremis*	596
1473	euthanized *in extremis*	644
1474	euthanized *in extremis*	363

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - FEMALE

Group, Animal Number	Fate	Day
1 mg/kg/day		
1475	terminal necropsy	706
1476	found dead	616
1477	euthanized *in extremis*	607
1478	euthanized *in extremis*	630
1479	euthanized *in extremis*	630
1480	euthanized *in extremis*	544
50 mg/kg/day		
1481	interim necropsy	369
1482	interim necropsy	369
1483	interim necropsy	369
1484	interim necropsy	369
1485	interim necropsy	369
1486	interim necropsy	370
1487	interim necropsy	370
1488	interim necropsy	370
1489	interim necropsy	370
1490	interim necropsy	370
1491	terminal necropsy	705
1492	euthanized *in extremis*	515
1493	found dead	467
1494	euthanized *in extremis*	703
1495	euthanized *in extremis*	655
1496	terminal necropsy	705
1497	euthanized *in extremis*	396
1498	euthanized *in extremis*	382
1499	euthanized *in extremis*	617
1500	terminal necropsy	705
1501	found dead	430
1502	euthanized *in extremis*	700
1503	euthanized *in extremis*	638
1504	euthanized *in extremis*	448
1505	euthanized *in extremis*	593
1506	found dead	439
1507	euthanized *in extremis*	426
1508	euthanized *in extremis*	617
1509	euthanized *in extremis*	645
1510	found dead	474
1511	euthanized *in extremis*	541

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - FEMALE

Group, Animal Number	Fate	Day
50 mg/kg/day		
1512	found dead	261
1513	euthanized *in extremis*	282
1514	euthanized *in extremis*	392
1515	euthanized *in extremis*	532
1516	terminal necropsy	705
1517	euthanized *in extremis*	546
1518	euthanized *in extremis*	174
1519	euthanized *in extremis*	555
1520	terminal necropsy	705
1521	euthanized *in extremis*	610
1522	euthanized *in extremis*	567
1523	euthanized *in extremis*	617
1524	euthanized *in extremis*	540
1525	euthanized *in extremis*	523
1526	euthanized *in extremis*	671
1527	euthanized *in extremis*	617
1528	terminal necropsy	705
1529	euthanized *in extremis*	444
1530	euthanized *in extremis*	540
1531	euthanized *in extremis*	596
1532	terminal necropsy	705
1533	euthanized *in extremis*	561
1534	found dead	587
1535	euthanized *in extremis*	525
1536	euthanized *in extremis*	387
1537	euthanized *in extremis*	574
1538	terminal necropsy	705
1539	euthanized *in extremis*	525
1540	euthanized *in extremis*	628
1541	terminal necropsy	706
1542	found dead	317
1543	terminal necropsy	706
1544	euthanized *in extremis*	526
1545	found dead	330
1546	terminal necropsy	706
1547	terminal necropsy	706
1548	euthanized *in extremis*	617
1549	terminal necropsy	706
1550	found dead	635

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - FEMALE

Group, Animal Number	Fate	Day
50 mg/kg/day		
1551	euthanized *in extremis*	469
1552	euthanized *in extremis*	359
1553	terminal necropsy	706
1554	euthanized *in extremis*	485
1555	found dead	325
1556	euthanized *in extremis*	350
1557	euthanized *in extremis*	662
1558	euthanized *in extremis*	617
1559	terminal necropsy	706
1560	euthanized *in extremis*	561
500 mg/kg/day		
1561	interim necropsy	369
1562	interim necropsy	369
1563	interim necropsy	369
1564	interim necropsy	369
1565	interim necropsy	369
1566	found dead	349
1567	died after dosing	349
1568	interim necropsy	370
1569	interim necropsy	370
1570	interim necropsy	370
1571	interim necropsy	370
1572	interim necropsy	370
1573	euthanized *in extremis*	680
1574	euthanized *in extremis*	512
1575	found dead	518
1576	terminal necropsy	705
1577	euthanized *in extremis*	607
1578	terminal necropsy	705
1579	euthanized *in extremis*	609
1580	euthanized *in extremis*	352
1581	terminal necropsy	705
1582	euthanized *in extremis*	625
1583[r]	euthanized *in extremis*	396
1584[r]	found dead	538
1585	terminal necropsy	705
1586	found dead	591
1587	terminal necropsy	705

[r] Replacement animal

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - FEMALE

Group, Animal Number	Fate	Day
500 mg/kg/day		
1588	euthanized *in extremis*	565
1589	euthanized *in extremis*	561
1590	euthanized *in extremis*	594
1591	found dead	593
1592	euthanized *in extremis*	630
1593	terminal necropsy	705
1594	terminal necropsy	705
1595	terminal necropsy	705
1596	found dead	392
1597	euthanized *in extremis*	649
1598	euthanized *in extremis*	590
1599	found dead	577
1600	euthanized *in extremis*	694
1601	found dead	483
1602	euthanized *in extremis*	591
1603	euthanized *in extremis*	617
1604	found dead	403
1605	euthanized *in extremis*	504
1606	euthanized *in extremis*	476
1607	terminal necropsy	705
1608	found dead	526
1609	found dead	690
1610	euthanized *in extremis*	320
1611	euthanized *in extremis*	617
1612	terminal necropsy	706
1613	terminal necropsy	706
1614	found dead	411
1615	found dead	546
1616	found dead	578
1617	euthanized *in extremis*	400
1618	terminal necropsy	706
1619	euthanized *in extremis*	672
1620	euthanized *in extremis*	630
1621	terminal necropsy	706
1622	found dead	670
1623	terminal necropsy	706
1624	euthanized *in extremis*	589
1625	found dead	581
1626	euthanized *in extremis*	588

Study Number

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Record of Animal Fate and Disposition - FEMALE

Group, Animal Number	Fate	Day
500 mg/kg/day		
1627	euthanized *in extremis*	396
1628	terminal necropsy	706
1629	found dead	631
1630	found dead	632
1631	terminal necropsy	706
1632	terminal necropsy	706
1633	terminal necropsy	706
1634	euthanized *in extremis*	630
1635	euthanized *in extremis*	462
1636	euthanized *in extremis*	537
1637	euthanized *in extremis*	609
1638	euthanized *in extremis*	672
1639	found dead	201
1640	euthanized *in extremis*	610